MINIREVIEW

Anti-Apoptotic Actions of Cytokines in Mammalian Cells (44379)

BHALOO J. DESAI AND HELEN E. GRUBER[1]

Department of Orthopaedic Surgery, Carolinas Medical Center, Charlotte, North Carolina 28232–2861

Abstract. **Apoptosis is now widely recognized as an important mode of cell death. Since the apoptotic pathway is an active process, modulation of apoptosis is important in our understanding of cell pathophysiology. Recent data have shown the inhibition of apoptosis in different cell types exposed to certain cytokines. Therapeutics that modulate the regulation of apoptosis provide an opportunity for the treatment of certain diseases. There are many reviews for apoptosis induction and the regulators involved. The present report selects important articles on the recent data showing the anti-apoptotic ability of cytokines in mammalian cells. Other novel compounds showing anti-apoptotic functions are also reviewed.** [P.S.E.B.M. 1999, Vol 221]

This review article focuses on agents and cytokines with anti-apoptotic functions. Apoptosis is now widely recognized as an important mode of cell death whereby environmental or developmental stimuli activate a genetic program for a specific series of events that result in death of a cell (1). Many cells undergo apoptosis (programmed cell death) during normal development (1); in most mammalian tissues this process continues throughout life. Although the mechanism of apoptosis is still not completely understood, evidence indicates its conservation in evolution from nematode worms to humans (2). Apoptosis differs from necrosis, which results from physical injury and is typified by cytoplasmic organelle destruction and loss of plasma membrane integrity (3). Apoptosis is associated with cytoplasmic blebbing, chromatin condensation, and nuclear DNA fragmentation (4).

In addition to morphologic nuclear changes, an important biochemical hallmark of apoptosis is fragmentation of DNA into discrete 180–200 base-pair fragments (4). Internucleosomal DNA cleavage is preceded by the formation of high-molecular-weight DNA fragments; the relationship between the formation of these large fragments (700-, 300-, and 50-kilobase-pair) and oligonucleasomal DNA laddering represents both precursor and product (5). Identification and evaluation of DNA fragmentation thus serves as the basis for many apoptotic analytical methods including *in situ* hybridization and flow cytometry.

Induction and Inhibition of Apoptosis

Many regulators of apoptosis fall into two categories: developmental cues or environmental cues. Of the former, proper regulation depends both on survival factors and death factors. Cell viability is promoted by survival factors both *in vivo* and *in vitro* and is critical for normal development (6). Absence of survival factors induces apoptosis (6). Many studies and reviews are available for apoptotic inducers (1, 2); this will not be a subject covered in detail in this review.

The subject of this review is the wide variety of recognized inhibitors of apoptosis with specific focus on genetic regulators of apoptosis and the anti-apoptotic actions of cytokines. Study of these inhibitors advances our understanding of apoptosis and its relationship to malignancy.

[1] To whom requests for reprints should be addressed at Orthopaedic Research Biology, Cannon 3rd Floor, Carolinas Medical Center, P.O. Box 32861, Charlotte, NC 28232–2861. E-mail: hgruber@carolinas.org

0037-9727/99/2211-0001$14.00/0

Significance of Apoptosis in Health and Disease

All mammalian cells have the ability to initiate necessary signaling and processing pathways to undergo apoptosis. It is now well understood that apoptosis is essential for normal development (6). Apoptosis is thought to have many regulatory points within the apoptotic cascade between pro-apoptotic and anti-apoptotic events; thus, improper regulation is now believed to lead to disease states such as hepatic disorders (7) and neoplasia (8).

Therapeutics that modulate the regulation of apoptosis provide an opportunity for the treatment of certain diseases. Inhibition of apoptosis may aid the process of tissue repair by promoting cellular proliferation and tissue regeneration and influence diseases caused by apoptotic cell death. Apoptosis induction may prove useful in treating malignant neoplastic cells and autoimmune diseases by causing destruction of tumor cells (9). A direct link of apoptosis to specific disease states, such as lymphoproliferation and lupus-like disease (10) and cancer due to loss of p53 function or gain of Bcl-2 (8) has been established. This continues to be an exciting area of research as we identify genes that regulate apoptosis and various diseases. Before discussing the many agents shown to inhibit apoptosis, we will briefly review the main genetic regulators of apoptosis. The role of these agents has become important in the investigation of the inhibitory effects of agents on apoptosis.

Genetic Regulators of Apoptosis

Some components of cell death machinery appear to be shared by most cell types. Regulation can be conceptualized as involving the signaling pathways initiating apoptosis, the processing machinery executing the apoptotic process, and the molecules that inhibit apoptosis (11). Different signaling pathways ultimately may converge to activate a common apoptotic path, and hence genes and proteins involved in apoptosis are signal sensors, signal transducers, regulators, and adapters. We will discuss briefly the main players in apoptosis regulation.

The NGF-TNF Receptor Family, and Fas/Fas L Genes. Signal sensors are devoid of catalytic activity, but they recruit catalytic enzymes (protein kinases) that transduce the death signal. Some examples of signal sensors are members of the nerve growth factor/tumor necrosis factor receptor family and include Fas, TNF-R1, or CD30 (12). The cell surface receptor Fas is the best-understood component in the pathway of apoptosis. The Fas ligand (FasL), produced by the immune system, binds to Fas and activates a death program (10).

Ced Genes and the ICE Family of Cysteine Proteases. The genes regulating apoptosis were initially discovered in the nematode *Caenorhabditis elegans.* During its development, the generation of 959 somatic nuclei is accompanied by the generation and eventual death by apoptosis of 131 cells (13). Apoptosis is controlled by two genes (*ced*-3 and *ced*-4), and the cloning of the former shows a strong homology to human interleukin-1β converting enzyme (ICE), a cysteine protease enzyme (2). Many cysteine proteases have been identified in mammals. The activity of one or more is increased by apoptosis (14, 15). Members of the ICE protease family continue to be identified; recently *ced*-9 has been shown to protect cells from apoptosis in *C. elegans* (1). The mechanism for mammalian apoptotic cell death is thought to require specific proteolytic degradation, since inhibitors of the ICE family inhibit apoptosis (for example, cowpox serpin) (16).

Bcl-2 Family of Genes. There are two sources of apoptosis inhibitors: genes present in the genome that become improperly regulated during oncogenesis and genes derived from viruses (2). One of the oncogenic genes, Bcl-2, functions by inhibiting apoptosis (17). This gene is the founding member of a multigene family whose members have one of two functional properties: either inhibition of apoptosis or promotion of apoptosis. Inhibitors of apoptosis include Bcl-L (18), adenovirus E1B 19K (19), Mcl-1 (20), and Al (21). Inducers of apoptosis include Bax (22), Bak (23) and Bcl-xS (18). Bcl-2 family members interact and can form both homodimers and heterodimers. Apoptosis inhibitors associate with the apoptosis promoters, suggesting an antagonistic relationship (22). It has been shown that Bcl-2 interacts with Bax, thus excess of Bax relative to Bcl-2 promotes cell death whereas excess of Bcl-2 relative to Bax promotes survival (22). A similar relationship has been observed between Bcl-2 and the other promoters of apoptosis in this family (18, 23). Some evidence suggests that Bcl-2 family members can also interact with classical signal transduction molecules such as *ras* (24).

p53. One of the most important regulators of the cell cycle is the tumor suppressor protein p53. A large body of evidence suggests that it also plays a role in the apoptosis process. DNA damage induces p53 (25). Thymocytes from animals lacking the p53 gene, however, do not undergo apoptosis in response to DNA-damaging agents such as irradiation or etoposide (26, 27). p53 is a regulator of Bcl-2 and bax gene expression *in vitro* and *in vivo* (28), and appears to be a transcriptional silencer for the Bcl-2 gene (29).

c-*myc* Gene. Another transcription regulator, c-*myc*, has been shown to cause apoptosis. The gene is similar to the p53 gene but is also cell-type and stimulus specific (30). Generally, expression of c-*myc* induces cells either to proliferate or undergo apoptosis, depending on the presence of other survival factors (31, 32). Several studies have demonstrated that Bcl-2 can prevent c-*myc* induced cell death (31, 33).

Inhibiting Agents of Apoptosis

A wide variety of inhibitors of apoptosis are now identified, and new ones continue to be studied. Identification of these agents is very important in advancing our understanding of the role between malignancy/disease and apoptosis. Many of these inhibitors under differing conditions can act as inducers. Table I highlights several known inhibitory

agents; these are not cytokines/growth factors and are mentioned here for general interest; the reader is referred to the references provided for additional information.

It is well known that growth factors can function to prevent apoptosis, primarily due to the fact that growth factor withdrawal induces apoptosis (6). Figure 1 below outlines the apoptotic pathway with and without growth factor presence. Work has progressed, and now certain growth factors and cytokines have been shown to induce true anti-apoptotic signals. An overview of some of these cytokines and their anti-apoptotic abilities follows.

Insulin-Like Growth Factor Family (IGF). IGF-I and the family to which it belongs exert multiple biological actions in cells. Tissue development and growth require a balanced regulation of cell replication and death; inhibition of apoptosis by IGF-I is thought to play an important role in maintaining cell survival. Several studies have demonstrated the role of the IGF-I receptor and its ligands IGF-I and IGF-II in modulating apoptosis. Harrington *et al.* (32) studied inhibition of c-*myc* induced apoptosis in fibroblasts by IGF-I and IGF-II. Rat fibroblasts constitutively expressing a c-*myc* chimera, *myc*-ER was induced into apoptosis by the activation of c-*myc* with oestradiol in serum-free media. Addition of IGF-I and IGF-II significantly suppressed apoptosis. A later study with IGF-I showed that the suppressive effect on c-*myc* induced apoptosis in fibroblasts was not linked to the growth status of the cells. The anti-apoptotic signal persisted in the presence of protein synthesis inhibitors. This indicates that the IGF-I effects are not dependant upon induction of apoptosis repressor genes (32).

Inhibition of apoptosis by IGF-I and IGF-II has been shown in human colonic epithelial cells (61). The study used an adenoma cell line RG/C2 and tested IGF-I and IGF-II in serum-and growth factor–deprived conditions. Both IGF-I and IGF-II protected against apoptosis induced by serum withdrawal; IGF-I was more potent. This response was independent of c-*myc* since serum and growth factor withdrawal from RG/C2 cultures resulted in a rapid reduction in levels of c-*myc*.

The effect of IGF-I and IGF-II on osteoblast survival has also been reported (62). Mouse osteoblasts were cultured in the presence of IGF-I and IGF-II, and cell survival was assessed. Both IGFs enhanced the survival of osteoblasts by inhibiting apoptosis. IGF-I effects were more potent than those of IGF-II. Effects were mediated through the IGF-I receptor. The role of the IGF-I receptor in apoptosis has also been demonstrated in other studies (63, 64). Apoptosis is induced by the expression of a dominant negative mutated IGF-I receptor (63), and suppressed in cell lines that overexpress the IGF-I receptor (64). The IGF-I receptor has shown anti-apoptotic action in BALB/c3T3 cells induced into apoptosis by a topoisomerase I inhibitor etoposide (65). Both IGF-I and its receptor have inhibited TNF–induced apoptosis in these cells; this action was shown to be reversed by ethanol administration (66).

An early study showed that IGF-I prevented DNA fragmentation and apoptotic cell death in interleukin-3 (IL-3)–dependent hemopoietic cells (67). Apoptosis of human erythroid progenitor cells is also inhibited by IGF-I. A reduction in the amount of DNA breakdown occurred to 38%–46% (68).

Apoptosis in response to acute injury by ischemia/reperfusion has been inhibited by IGF-I in several studies. Buerke *et al.* (69) examined the cardioprotective effects of IGF-I in a murine model of myocardial ischemia reperfusion. IGF-I significantly weakened the incidence of myocyte apoptosis after myocardial ischemia and reperfusion. Similarly, two studies showed the inhibitory effects of IGF-I in stroke-prone, spontaneously hypertensive rats (SHRSP) (70, 71). In the first study cortical neurons from SHRSP were isolated and assessed for apoptosis after nitric oxide and N-methyl-D-aspartate neurotoxic agent treatment. Both agents caused apoptosis in these cells; however, treatment with IGF-I rescued neurons from cell death (70). In addition, a P13-kinase inhibitor (wortmannin) lessened the protective effect of IGF-I; the authors suggested that this reflected inadequate activation of signaling pathways downstream of protein tyrosine kinases (70).

The second study looked at apoptosis in neurons from SHRSP after cerebral ischemia was followed by reperfusion (71). Apoptosis was induced, but pretreatment with IGF-I reduced the number of apoptotic neurons in SHRSP with cerebral ischemia followed by reperfusion. Apoptosis induced by the protein synthesis inhibitors cycloheximide and ricin in MDA-231 cells was inhibited, and cell survival was enhanced by addition of IGF-I (72). Tumor progression in p53-deficient mice was inhibited by dietary restriction. Supplementation with IGF-I abrogated the protective effect of dietary restriction on cancer progression due to the growth-factor inhibitory effects on apoptosis (73).

The studies mentioned above demonstrated the ability of IGF-I to inhibit apoptosis and hence influence disease states and injury. Some studies have elucidated the regulatory genes and signaling pathways involved in IGF-suppressed apoptosis. Parrizas *et al.* (74) showed that IGF-I exerts its inhibitory effects on apoptosis using the phosphatidylinositol 3′-kinase and mitogen-activated protein kinase pathways in PC12 cells. IL-3 dependent murine myeloid progenitor cells showed increased apoptosis after serum withdrawal and 80% reduction in the endogenous expression of Bcl-2 (75). Addition of IGF-I reduced apoptosis by maintaining the levels of Bcl-2/Bax heterodimers; this suggests that Bcl-2 is an important agent in the signaling pathway used by IGF-I (75). IGF-I was also shown to reduce apoptosis in serum-deprived PC12 cells by upregulation of Bcl-xL messenger RNA and protein levels (76). In H9C2 cardiac muscle cells, IGF-I inhibited apoptosis by weakening Bax induction and activating caspase-3 (77). Drug-induced apoptosis in HBL100 human breast cancer cells was inhibited by IGF-I, but changes in Bcl-2 or Bax were not detected (78). Involvement of interleukin-1β converting

Table I. Agents with Reported Anti-apoptotic Capabilities

Agent	Cell type/reference	Result	Comments
Polyamines	Cerebellar granule neurons (34)	Prevented apoptotic neuronal cell death	Prevented apoptotic cell death through NMDA receptor dependent and independent mechanism
Vitamin E homologs	Rat PC12 cells (35)	Prevented hyperoxia-induced apoptosis	α-Tocopherol was the most effective inhibitor
Peptide inhibitors	AK-5 tumor cells (36)	Inhibited dexamethosone or serum factor-induced apoptosis	Acidification that occurred during apoptosis was also abolished
Nitric oxide	Hepatocytes (37)	Inhibited serum withdrawal- or tumor necrosis factor α- or anti-*Fas* antibody-induced apoptosis	Effect was *via* either directly or indirectly inhibiting caspase-3-like activity
	Human leukocytes (38)	Inhibited *Fas*-induced apoptosis	Inhibition was via a cGMP-independent mechanism
Dexamethasone	Neonatal rat model (39)	Pretreatment with dexamethasone prevented apoptosis of hypoxic-ischemic encephalopathy	Inhibited induction of c-*fos* transcription
	Human gastric cancer TMK-1 cells (40)	Delayed apoptosis	Enhanced basal levels of Bcl-x gene expression
Zinc	Molt4 leukemia cells (41) See also review by Fraker and Telford (42)	Inhibited apoptosis	Zinc inhibited the apoptotic protease caspase-3
Anti-oxidants	Human promyelocytic cell line; HL-60 (43)	Prevented serum-induced apoptosis	Effect was independent of Bcl-2 content
	Rat thymocytes (44)	Prevented etoposide, thapsigargin-induced apoptosis	Anti-apoptotic effect occurred if cells were pre-incubated with ascorbate for 1 hr
1,25-Dihydroxy-vitamin D_3	Human leukemia cells; HL60 (45)	HL60 cells were protected from apoptosis	Also caused an increase of anti-apoptotic protein Mcl-1, A1, and RAF-1 and a decrease in cytochrome c release
Arachidonic acid Polyunsaturated fatty acids	Rat W256 carcinosarcoma cells (46)	Suppressed nordihydroguaiaretic-induced apoptosis	These reagents may enhance tumor growth due to their anti-apoptotic effect
Calcium channel blockers	Human aortic smooth muscle cells (47)	Inhibited 25-hydroxy-cholesterol-induced apoptosis	Calcium influx through plasma membrane channels was an important signal in oxysterol-induced apoptosis
	Rat seminiferous tubules (48)	Protected against methoxyacetic acid–induced spermatocyte induced apoptosis	Protective effect via interactions with calmodulin or protein kinase C
	Rat kidneys (49)	Reduced renal apoptosis during ischemic reperfusion	Anti-apoptotic effect occurred if kidneys were pretreated with calcium channel blocker
ER/SR calcium-ATPase inhibitors	IL-3 dependent cell line (50)	Suppressed IL-3 deprivation-induced apoptosis	Anti-apoptotic effect was due to induction of IL-4 release
Vasoactive intestinal peptide and pituitary adenylate cyclase activating polypeptides	Rat thymocytes (51)	Prevented spontaneous and dexamethasone-induced apoptosis	Neuropeptides may be involved in intrathymic T-cell maturation
Curry pigment; curcumin	Human and rat lymphocytes (52)	Prevented dexamethasone-induced apoptosis	Anti-apoptotic effect may involve modulation of the AP-1 transcription factor
Retinoic acid	Murine hematopoietic cell line; Y6 (53)	Inhibited IL-6-induced apoptosis	Stopped down regulation of c-*myc* gene by IL-6
Mutagen; 2-amino-3-methylimidazol [4,5-*f*]quinoline	Rat colon (54)	Tumors induced by this agent caused inhibition of apoptosis	Inhibition was due to increased levels of Bcl-2 and decreased levels of Bax
R-Deprenyl	Cerebellar granule neurons (55)	Prevented cytosine arabinoside-induced apoptosis	May act by preventing p53-dependent apopotosis

Table I. Continued

Agent	Cell type/reference	Result	Comments
Bioflavonoid quercetin (anti-cancer agent)	Glomerular mesangial cells, epithelial cells, and fibroblasts (56)	Prevented hydrogen peroxide induced apoptosis	Effect was due to suppression of the tyrosine kinase-c-*Jun*/AP-1 pathway
Thrombo-poietin	Murine hematopoietic progenitor cells (57)	Inhibited apoptosis	Also promoted viability of cells comparable to IL-1 and granulocyte colony-stimulating factor
Transcription factors	T lymphocytes, human leukemia cells (58, 59, 60)	Inhibited apoptosis	

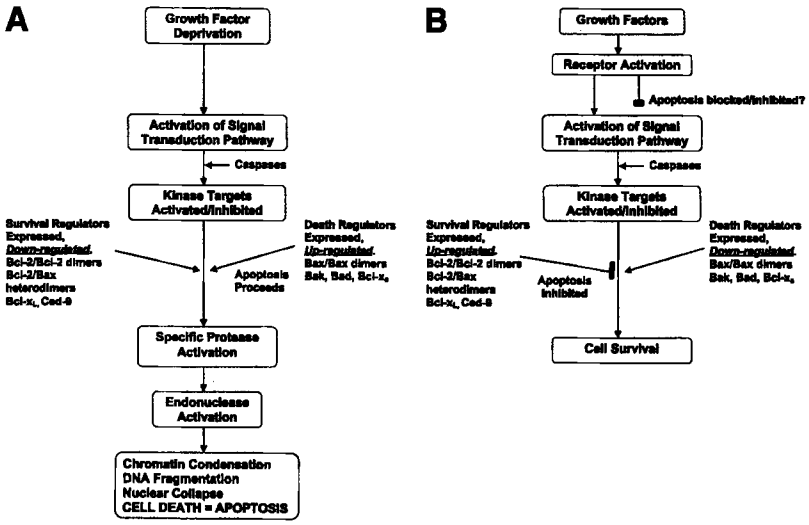

Figure 1. Diagrammatic representation of major points in the pathway regulating apoptosis. Shown are schemes hypothesized for (A) growth factor deprivation and (B) growth factor addition.

enzyme like protease (ICE) in cell death and its suppression by IGF-I have been demonstrated in mammalian cell lines (79) and in cerebellar external granular layer neurons (80). Induction of apoptosis by N-*myc* expression in hepatocytes (81) and woodchuck liver epithelial cells (82) has been blocked by IGF-II.

These studies show the diverse inhibitory effects of IGF on apoptosis and the regulatory genes involved. Future studies will further elucidate the important role of this growth factor in the apoptotic process.

Platelet-Derived Growth Factor (PDGF). PDGF is a potent mitogen *in vitro* (83), and it also signals other cellular responses such as survival (84) and transformation (85). This growth factor is present at detectable levels in fetal calf serum and hence may exert anti-apoptotic effects on cell growth. Few studies to date have evaluated PDGF and its anti-apoptotic effects. Harrington *et al.* (32) examined the effect of PDGF on c-*myc*–induced apoptosis in fibroblasts. PDGF suppressed apoptosis in these cultures at levels similar to that found by fetal calf serum. PDGF alone was not able to suppress apoptosis in c-*myc*–expressing fibroblasts during prolonged periods of serum deprivation. The protection of c-*myc*–induced apoptosis by PDGF did not result in any change of the Bcl-2 protein or in Bcl-2 post-translational modification (32). PDGF was able to inhibit tumor necrosis factor–induced cell death in conjunction with IGF-I in BALB/c3T3 cells for up to 5 days, whereas in the absence of PDGF, IGF-I was only effective for 2 days (86). The effect of PDGF in combination with IGF-I and IGF-II on osteoblast survival has also been reported (62). PDGF alone had no effect on osteoblast survival; however, PDGF potentiated the survival-promoting effects of both IGF-I, IGF-II and insulin in mouse osteoblasts (62). PDGF alone has also been shown to have anti-apoptotic effects. In human vascular smooth muscle cells derived from coronary plaques and normal coronary arteries and aorta, PDGF was identified as a potent anti-apoptotic survival factor (87). PDGF-BB was shown to enhance cell survival and cell cycle progression in skeletal myoblasts in culture although this peptide was not able to promote differentiation in these cells (88). Funa *et al.* (89) examined a mouse neuroblastoma cell line, NB41, for its response to PDGF. NB41 cells showed apoptosis on serum withdrawal, which was further enhanced by the addition of neurotoxin, 6-hydroxy dopamine (6-OHDA), however, addition of PDGF-BB prior to 6-OHDA addition resulted in cells rescued from undergoing apoptosis (89). An association between PDGF effects and the regulatory gene involved has also been demonstrated (90). In liver progenitor cells PDGF-mediated cell survival from apoptosis was enhanced by BAG-1 due to its association with the PDGF receptor (90). Association of the receptor with BAG-1 was shown to

be mediated by both the N- and C-terminal domains of BAG-1 (90).

Epidermal Growth Factor (EGF)/Transforming Growth Factor (TGF) Family. EGF is an important mitogenic stimulus *in vitro* and its role in apoptosis has been studied extensively. EGF was able to block the apoptotic effects of the inflammatory cytokines tumor necrosis factor-α (TNF-α) and γ-interferon (INF-γ) in human cytotrophoblasts and syncytiotrophoblasts from normal-term placenta (91). Since EGF is abundantly expressed in maternal and fetal tissues, the anti-apoptotic signal shown by this growth factor suggests a novel role for EGF in normal placental development (91). Apoptotic cell death has been suggested as a possible cause of degeneration of ovarian follicles during atresia. To determine whether EGF could inhibit this cell death, Tilly *et al.* (92) evaluated apoptosis in ovarian granulosa cells or intact follicles placed in serum-free media and found that EGF inhibited the spontaneous onset of apoptotic DNA cleavage in cultures by 40%–60%. This effect was based on a tyrosine-kinase–dependent mechanism. EGF has also been shown to play a role in tumorigenicity by reducing apoptosis. In *ras*-stimulated epithelial cells EGF, transforming growth factor-β and heparin-binding EGF-like growth factor increased proliferation and resistance to apoptosis (93). In human glioblastoma cells a mutant epidermal growth factor receptor (de 2-7 EGFR) enhanced tumorigenicity by increasing proliferation and inhibiting apoptosis by virtue of constitutive activation of its tyrosine kinase (94). Apoptosis induced by the protein synthesis inhibitors cycloheximide and ricin in MDA-231 cells was inhibited, and cell survival was enhanced by addition of EGF (72). This effect was blocked by the protein kinase C inhibitor staurosporine, suggesting the involvement of protein kinase C in the MDA-231 cell death pathway (72). In an astrocyte progenitor cell line (AP-16), EGF deprivation resulted in apoptosis (95). In the absence of EGF, AP-16 cells were prevented from undergoing apoptosis by TGF-α and basic fibroblast growth factor (95). Epithelial cells from human colon have been shown to undergo apoptosis in response to inhibition of intercellular contact by anti-integrin antibodies (96). Hague *et al.* (61) investigated whether specific cytokines were able to act as survival factors for colonic epithelial cells (RG/C2). EGF acted as a survival factor and protected cells from apoptosis after growth factor withdrawal. The apoptosis observed in these cells was independent of c-*myc* and p53 (61).

Apoptosis in the developing tooth is thought to be responsible for anomalies such as cleft lip and palate (97). EGF was investigated for its role in apoptosis of cultured dental tissues and found to prevent apoptosis on dental mesenchyme (98).

TGF-β, a physiological inhibitor of epithelial cell proliferation, has been shown to induce apoptosis in fetal hepatocytes in primary culture (99). This effect was blocked by the mitogenic stimuli of EGF and thought to occur by the prevention of c-*fos* induction (99). The authors suggest that EGF may play an important role during early liver development by acting as an important mitogen and allowing cells to overcome apoptosis and differentiate.

The inhibitory effects of the TGF family on apoptosis are also important. In human leukemic HL-60 cells, apoptosis induced by cell densities higher than 10^6/ml was inhibited by TGF-β1 (100). The apoptosis observed in these cells was independent of ICE but was strongly affected by signaling events through the TGF-β1 receptor and by the action of Bcl-2 (100). Apoptosis induced by the membrane-permeable second messenger C2-ceramide in human leukemic HL-60 cells was inhibited by TGF-β1 by maintaining constant levels of Bcl-2 (101).

The anti-apoptotic effects of TGF-β1 have been investigated in degenerative disorders such as rheumatoid arthritis (102). Kawakami *et al.* (102) investigated the mitogenic and anti-apoptotic effects of TGF-β1 on rheumatoid synovial cells. TGF-β1 suppressed apoptosis of synovial cells from rheumatoid patients by inhibiting Fas expression and increasing Bcl-2 expression; a similar effect was observed in synovial cells from patients with osteoarthritis (102). The effect of TGF-β1 on Fas antigen expression is achieved at the transcriptional level (102). The authors suggested that this TGF-β1 effect resulted in the perpetuation of synovial hyperplasia in patients with rheumatoid arthritis (102).

TGF-β1 inhibition of Fas-mediated apoptosis has also been observed in murine bone marrow progenitor cells. TGF-β1 may act by protecting these cells from the increased Fas expression and function normally observed with a pro-inflammatory response (103). The anti-apoptotic activity of TGF-β has been observed in vascular smooth muscle cells isolated from the aorta of transgenic mice and is thought to be dependent on the catalytic activity of plasmin mediated by urokinase-type plasminogen activator (104). Suspension-induced apoptosis of cultured human keratinocytes was also protected by TGF-β1 and resulted in the decrease of steady state messenger RNA levels for c-*myc* (105).

The oncogene c-*myc* and TGF-α have frequently been co-expressed in human tumors (106). Overexpression of TGF-α transgene in c-*myc*/TGF-α hepatocellular carcinomas has been shown to reduce apoptosis dramatically and hence enhance survival of neoplastic cells (107).

Endothelin (ET). ET-1 is a potent vasoconstrictor as well as a mitogen (108). Recent studies describe ET-1 as an apoptosis survival factor for cultured rat endothelial cells (109) and human smooth muscle cells (110). Endothelial cells from rat aorta underwent apoptosis upon serum starvation. Serum starvation–induced apoptosis was suppressed by addition of ET-1 (109). The protective effect of ET-1 was blocked by the ET_B receptor antagonist (BQ788). The authors suggested that ET-1 functioned as an apoptosis survival factor for endothelial cells *via* the ET_B receptor (109). In a further study, the effect of ET-1 suppressing apoptosis

in rat endothelial cells was investigated (110). The anti-apoptotic effect of ET-1 in these cells confirmed the role of this growth factor as an autocrine/paracrine survival factor; however, these effects were shown not to be mediated through phospholipase C, tyrosine kinase, MAP kinase, or phosphatidylinositol-3 kinase (110). In human pericardial and prostatic smooth muscle cells, addition of ET-1 was shown to decrease paclitaxel-induced apoptosis (111). ET-1 has also been shown as a potent survival factor for c-*myc*-dependent apoptosis (112). Low doses of ET-1 protected fibroblasts against apoptosis induced by serum deprivation through a c-*myc*–dependent process and was mediated by the ET_A receptor (112). This effect was abrogated by inhibiting the mitogen-activated protein kinase pathway (112).

Nerve Growth Factor (NGF). NGF is a neurothrophic factor that maintains neuron survival (113). Several studies have examined the role of this factor in apoptosis. Kawamoto *et al.* (114) investigated the anti-apoptotic ability of NGF on rat peritoneal mast cells (PMCs). Addition of NGF decreased the number of apoptotic cells and prevented the characteristic DNA fragmentation. The NGF receptor p140trk was expressed on PMCs during the anti-apoptotic actions of NGF (114). Sympathetic neurons died by apoptosis in culture when deprived of NGF (115). This death was more rapid in sympathetic neurons isolated from Bcl-2–deficient mice after NGF deprivation than in neurons from wild-type mice. This suggests that Bcl-2 is an important regulator of neuron survival after NGF deprivation (115). Katoh *et al.* (116) have also shown the anti-apoptotic ability of NGF in rat pheochromocytoma (PC12) cells accompanied by an increase in the amount of Bcl-2. When neuronally differentiated PC12 cells underwent apoptosis on NGF deprivation, actinomycin D and cycloheximide-sensitive caspase (ICE-like) activity was induced (117). Forced expression of Bcl-2 or Bcl-2 binding protein, BAG-1, blocked the apoptosis induced by NGF withdrawal by preventing caspase activation (117). When NGF signaling was blocked in human keratinocytes by anti-NGF neutralizing antibody or K252 (a specific inhibitor of tyrosine kinase high affinity NGF receptor) apoptosis was induced in these cells (118). The anti-NGF antibody and K252 downregulated Bcl-2 expression; the authors suggested that NGF is an important survival factor for human keratinocytes *in vitro* and acts through a high affinity NGF receptor maintaining the levels of Bcl-2 (118).

NGF is able to overcome apoptosis induced by other agents. NGF withdrawal from PC12 cells results in apoptosis; this type of death increases on exposure of PC12 cells to S-100, a calcium binding protein. The presence of NGF in the culture medium, however, completely blocked the apoptotic effect of S-100 (119). In cerebellar granule cells *in vitro,* apoptosis induced by ethanol exposure was significantly reduced by the presence of NGF (120). This neuroprotective effect required protein and RNA synthesis (120).

NGF's potential as a therapeutic agent has been described for human diabetic retinopathy (121). Diabetes-induced apoptosis in rat retinal ganglion cells and Muller cells was prevented with NGF treatment (121).

Fibroblast Growth Factor (FGF) Family. Basic FGF (bFGF) is a pleiotropic cytokine that plays a role in mesodermal development (122) as well as in malignancy (123). Exposure of fibroblasts to bFGF increased cell survival by causing an increase in Mdm2 oncoprotein and inhibition of p53 function (124). Ureteric bud cells secrete several factors including bFGF, which rescues renal progenitors (precursors of tubular epithelia, capillaries, and cells that are involved in the growth of the ureteric bud) from apoptosis (125). In cerebellar granule cells, *in vitro* apoptosis induced by ethanol exposure was significantly reduced by the presence of bFGF (120).

Studies also describe bFGF's ability to delay apoptosis (126, 127). When human B-cell leukemia cell lines were treated with fludarabine alone, apoptosis occurred. In combination with bFGF, however, the result was prolonged survival (126). Bcl-2 protein levels increased upon addition of bFGF suggesting a role for this gene in the delay of fludarabine-induced apoptosis (126). The NIH 3T3 fibroblast–derived cell line expresses more immunoreactive bFGF as compared to the parental NIH 3T3 cells. Such cells exhibited delayed apoptosis upon serum withdrawal (127). This delay also resulted in an increase in cellular Bcl-2 levels (127).

Fibroblast growth factor-2 (FGF-2) has also been shown to inhibit apoptosis. Alanko *et al.* (128) have shown that FGF-2 inhibited apoptosis in human teratocarcinoma cells when cells were grown on a collagen substratum. In endothelial cells, growth factor and serum deprived–induced apoptosis was blocked by FGF-2 (129). Bcl-2 is induced by FGF-2 in these cells. Although FGF-2 anti-apoptotic actions were dependent on tyrosine phosphorylation, it did not result in MAP kinase pathway activation (129). The authors concluded that FGF-2 inhibited apoptosis in endothelial cells by Bcl-2–dependent and independent mechanisms.

Several studies have shown the anti-apoptotic effects of bFGF in retinal dystrophies (130–133). Retinal ischemia was induced in Wistar rats; bFGF and FGF-receptor (FGF-R) mRNA was observed in normal sensory retina following ischemia suggesting that bFGF has a protective role in the retina (130). Desire *et al.* (131) showed that the role of FGF-2 during chick retinal development was to stimulate neuron differentiation and protect neurons against cell death (131). Similarly, FGF-2–stimulated release of endogenous FGF-1 in retinal pigmented epithelial cells was shown to prolong cell survival due to inhibition of apoptosis in these cells (132). Liu *et al.* (133) have shown that preconditioning rats with bright light protects these animals from photoreceptor degeneration (133). The protective effect in rat retina was found to be due to a prolonged increase in bFGF and phosphorylation of extracellular signal regulated protein kinases (Erks) (133). Thus bFGF can serve as a therapeutic agent in retinal diseases.

Table II. IL Family Members Reported for their Anti-Apoptotic Abilities

Interleukin	Cell type	Result	Comments
IL-1	Immature thymocytes (134)	Inhibited T cell receptor–mediated apoptosis	Inhibition mechanism may involve protein kinase C activation
IL-1α and IL-6	Myeloid leukemia (M1) (135)	Inhibited induction of apoptosis by TGF-β1	Absence of TGF-β1 made M1 leukemia cells independent of this cytokine for cell viability and growth
IL-1β	Human monocytes (136)	Inhibited monocyte death	Inhibition only possible if sufficient level of cytokine maintained continuously in culture. IL-1β exerts autocrine and paracrine control of cell survival
IL-2, IL-4, IL-6, IL-13	Human leukemic CD5+ B cells (137)	Delayed apoptosis by delaying the accumulation of cells displaying reduced levels of Bcl-2	Cytokine plays role in pathogenesis of B cell malignancies by maintaining Bcl-2 levels
IL-2 and IL-15	Human lymphocytes (138)	Inhibited apoptosis	When cytokine-specific α chain receptor is blocked anti-apoptotic effect of IL-2 decreased
IL-2	Human antigen-specific T-cell clones (139)	Inhibited IL-2 deprivation apoptosis in TH0, Th1, and Th2 clones	Inhibition resulted in active proliferation and enhanced expression of p53, Rb, and Bcl-xL proteins
IL-2, and IL-4	Human T cells (140)	Inhibited dexamethasone-induced apoptosis	Inhibition occurred via inhibition of IκBα expression
IL-3	Bone marrow derived *Baf*-3 cells (141)	IL-3 deprivation lead to apoptosis; IL-3 presence inhibited apoptosis	Long-term survival correlated with induction of Bcl-X gene expression and was dependent upon MAP-kinase activation
IL-3	Myeloid cells (142)	Suppressed γ-irradiation induced apoptosis	Action was dependent upon *Jak* kinase activation
	IL-3-dependent cell lines; IC.DP (143)	Survival from apoptosis induced by IL-3 deprivation	IL-3 stimulated glucose transport, which aids suppression of apoptosis
IL-4	Peripheral blood B-cell chronic lymphocytic leukemia (B-CLL) cells (144); IL-4 inhibition of apoptosis in B-CLL cells has also been shown by Craig (145), Panayiotides (146)	Addition of IL-4 to culture medium decreased *in vitro* apoptosis	Also showed that IL-4 decreased apoptosis from normal B-cells. IL-4 exerted anti-apoptotic effects by inhibiting loss of Bcl-2
IL-4 and IL-10	Alveolar macrophages (147)	Apoptosis reduced by IL-4 after apoptosis was induced by Lipopolysaccharides (LPS)	
IL-5	Eosinophils (148)	Significantly inhibited apoptosis in culture	Inhibition was possible due to upregulation of Bcl-2 protein and mRNA expression
IL-6	Myeloid leukemic cells (149)	Inhibited wild-type p53-induced apoptosis	Tumor suppressor gene products may be involved in restricting precursor cell populations
	Multiple myeloma (MM) derived cell lines; RPMI-8226 and IM-9 (150)	Inhibited Fas-induced apoptosis	IL-6 modulated stress-activated protein kinase thought to be associated with Fas-induced apoptosis
	B-CLL cells (B-chronic lymphocytic leukemia cells (151)	Inhibited spontaneous apoptosis	IL-6 inhibited DNA synthesis in an autocrine fashion but prolonged cell survival
IL-7	Mouse malignant T-lymphoma cells (152)	Inhibited apoptosis caused by separation of T-lymphoma CS-21 cells from CA-12 lymph node stromal cells	IL-7 suppressed CPP32-like protease activation resulting in Bcl-2 expression

Table II. Continued

Interleukin	Cell type	Result	Comments
IL-8	Human neutrophils (153)	Inhibited spontaneous and tumor necrosis factor α-induced apoptosis	IL-8 prolonged neutrophil survival by delaying apoptosis; this was mediated via the IL-8 receptor RII and was Bcl-2 independent
IL-10	T cells (154)	Inhibited apoptosis mediated by parainfluenza virus type 3 (PIV3)	PIV3 induced peripheral blood mononuclear cells to produce IL-10
IL-11	Mice small intestinal mucosa (155)	Partially suppressed apoptosis	IL-11 also increased mitosis frequency and proliferating cell nuclear antigen expression in intestinal crypt cells
IL-13 and IL-4	Human B lymphocytes (156)	Inhibited spontaneous apoptosis of peripheral blood B cells	Inhibition by IL-13 was possible when combined with CD40 ligand and resulted in upregulation of Bcl-xL and Mcl-1. IL-4 alone was able to inhibit apoptosis
	B chronic lymphocytic leukemia cells (B-CLL) (157)	Inhibited spontaneous apoptosis *in vitro*	Inhibition of IL-13 was not as potent as IL-4
IL-15	Human T and B cells (158)	Inhibited anti-Fas, anti-CD3, dexamethasone, and anti-IgM induced apoptosis	*In vivo* lethal multisystem apoptosis in mice induced by anti-Fas was suppressed by IL-15-IgG2b fusion protein. IL-15 was a general inhibitor of apoptosis *in vitro* and *in vivo*

Interleukin Family. There are many reports on the anti-apoptotic effects of various members of the interleukin (IL) family. These are described in Table II.

Concluding Remarks

Apoptosis is now widely recognized as an important mode of cell death. The goal of this article was to review the anti-apoptotic actions of specific cytokines on mammalian cells from 1991 to 1998. Many cytokines have now been studied for their anti-apoptotic actions in the hope of their use in therapeutic modalities. Progress continues in the effort to identify inhibitory agents of apoptosis and the regulatory molecules involved. Important advances include the role of cytokines in cancer therapy. Many neurodegenerative diseases are characterized by a loss of specific cells or cell populations. Thus, in disorders such as amyotrophic lateral sclerosis (ALS), Huntington's disease, Parkinson's disease, and Alzheimer's disease, cells are assumed to be lost *via* apoptosis. Inhibition of apoptosis by growth factors, such as NGF, the TGF-β family, and the IGF family, may be important in these disorders since all have been shown to influence neuronal survival (159, 160). Similarly, impaired development of the immune system, such as changes occurring in AIDS or leukemia due to excessive cell death by apoptosis, may benefit by manipulations of the apoptosis pathway with cytokine intervention such as the interleukin family (161). Studies of anti-apoptotic agents are also valuable because they add insight into the potential regulatory mechanisms of apoptosis.

We thank Deborah Venne for assistance in manuscript preparation. Due to the large body of apoptosis literature, and space limits, we are unable to cite and discuss many anti-apoptotic papers; we apologize to these authors.

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