Transcriptional regulation of the \textit{bcl-x} gene encoding the anti-apoptotic Bcl-x\textsubscript{L} protein by Ets, Rel/NF\textsubscript{κ}B, STAT and AP1 transcription factor families

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**Summary.** Transcription factors play an essential role in determining the fate of a cell by affecting the expression of target genes involved in proliferation, in differentiation and in programmed cell death. Under certain conditions, some of these factors are capable of deregulating expression of genes involved in the cell cycle and/or in programmed cell death resulting in uncontrolled proliferation of the cell. The focus of this review is on the transcriptional regulation of the \textit{bcl-x} gene encoding the anti-apoptotic Bcl-x\textsubscript{L} protein. Since 1999, several papers have implicated members of the Ets, Rel/NFκB, STAT and AP-1 families as transcription factors regulating \textit{bcl-x} expression. A specific emphasis of these different transcription factor families on \textit{bcl-x} regulation in hematopoietic cells is discussed.

**Key words:** \textit{bcl-x}, Promoter, Regulation, Transcription factors, Review

**Introduction**

Programmed cell death by apoptosis is a process essential for normal development and maintenance of cell homeostasis in organisms. Proteins of the bcl-2 family have been identified as initiators or inhibitors of apoptosis. The balance in the levels of expression of pro-apoptotic versus anti-apoptotic members is crucial in determining the fate of a cell: a more abundant expression of an anti-apoptotic member will permit a cell to survive whereas a higher expression of a pro-apoptotic member will induce apoptosis upon activation by a variety of apoptotic signals.

Anti-apoptotic members include Bcl-2, Bcl-x\textsubscript{L} (Boise et al., 1993), Bcl-w (Gibson et al., 1996), A1 (Lin et al., 1996) and Mcl-1 (Kozopas et al., 1993). Bcl-2, the first anti-apoptotic member identified, and the closely related Bcl-x\textsubscript{L} are probably the best characterized. Their genomic structures are similar and are believed to have arisen from a common ancestral gene or by gene duplication (Grillot et al., 1997). By maintaining the integrity of mitochondria, Bcl-2 and Bcl-x\textsubscript{L} inhibit cleavage-mediated activation of the caspase cascade which functions as the ultimate downstream effector pathway of the suicide program degrading proteins necessary for nuclear and cell integrity. Until recently, little was known about how these genes are regulated. In this review, we will focus on the transcriptional regulation of one member of the anti-apoptotic family, Bcl-x\textsubscript{L}.

**Bcl-x**

The \textit{bcl-x} gene encodes several alternatively spliced messenger RNAs including \textit{bcl-x}L, \textit{bcl-x}S, bcl\textsubscript{ΔTM} and \textit{bcl-β} (Shiraiwa et al., 1996; Grillot et al., 1997). Bcl-x\textsubscript{L} suppresses whereas Bcl-x\textsubscript{S} induces apoptosis (Boise et al., 1993; Fang et al., 1994; Gonzalez-Garcia et al., 1994). The functions of the other two transcripts have not yet been well documented. Bcl-x\textsubscript{L} is believed to be the key anti-apoptotic protein expressed in hematopoietic lineages including myeloid precursors and macrophages (Lotem and Sachs, 1995; Chatterjee et al., 1997; Packham et al., 1998; Sevilla et al., 1999), lymphoid cells of the pre-B lineage (Fang et al., 1994; Grillot et al., 1996), and double positive CD4+CD8+ T cells (Grillot et al., 1995; Ma et al., 1995). Bcl-x\textsubscript{L} expression is activated in B cells of the germinal center and in mature resting B and T lymphocytes after activation with mitogens and costimulatory signals (Broome et al., 1995; Grillot et al., 1996). Interestingly, pro-apoptotic Bcl-x\textsubscript{L} is not detected in murine T or myeloid cells (Gonzalez-Garcia et al., 1994; Packham et al., 1998; Sevilla et al., 1999). The importance of Bcl-x\textsubscript{L} in hematopoiesis has been confirmed by \textit{bcl-x} gene disruption studies in mice which die at E12-13 of embryonic development due to massive neuronal and hematopoietic progenitor apoptosis (Motoyama et al.,

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In addition to their roles in proliferative and differentiation pathways, several studies suggested that ets family members might affect the survival of cells. Apoptosis was observed in ets1-deficient T cells from chimera mice generated by ets1 gene disruption in embryonic stem cells with RAG2-/- blastocysts using the recombination activating gene complementation assay (Bories et al., 1995; Muthusamy et al., 1995). In other studies, Jin et al., reported that primary peritoneal macrophages obtained from "dominant negative" Δets2 transgenic animals died rapidly by apoptosis when depleted of CSF-1 (Jin et al., 1995), a factor necessary for the growth, differentiation and survival of myeloid cells. Finally, other experiments using PU.1/Sp1.1 showed that PU.1/Sp1.1 cooperated with an activated erythropoietin receptor (EpoR) to inhibit apoptosis in primary erythroblasts (Tran Quang et al., 1997). Taken together, these observations suggested that the role in inhibiting programmed cell death may be a common function of members of the ets family, yet the mechanism(s) of this inhibition have not be elucidated in these studies.

Like Bcl-xL, PU.1/Sp1.1 is expressed in hematopoietic precursors and in mature macrophages and pu.1 -/- mice are devoid of mature B cells, neutrophils or macrophages (Scott et al., 1994; Mckercber et al., 1996). Ets1 and Ets2 are specifically and reciprocally expressed during precise stages of thymic development (Pognonec et al., 1987, 1988; Bhat et al., 1989, 1990). Bcl-2 and Bcl-xL are expressed in a reciprocal manner during T cell development and interestingly, Ets2 and Bcl-xL were coexpressed in the same population of developing T cells. Coexpression of Ets2 and Bcl-xL is not limited to double-positive CD4+CD8+ T cells since both are also coexpressed in primary bone marrow macrophages (BMM) derived from bone marrow progenitor cells and in BMM upon activation of functional competence signals (Sevilla et al., submitted).

Transient expression of Ets2 in human 293 cells upregulates Bcl-xL protein expression (Sevilla et al., 1999). Constitutive expression of Ets2 in a CSF-1-dependent macrophage cell line (BAC1.2F5) also upregulates Bcl-xL expression in a constitutive manner and renders these cells resistant to apoptosis when depleted of CSF-1 (Sevilla et al., 1999). The most plausible mechanism of upregulation of Bcl-xL by Ets2 was by transcriptional activation.

Both the 5' regulatory sequences found upstream of the first noncoding exon of bcl-x and the first facultative intron contain potential EBS for Ets transcription factors. Eight EBS are found within a 700 bp fragment of the human promoter upstream of the first non-coding exon and one in the first intron (Fig. 1), while the predicted number of EBS found in a random 700 bp sequence is 1.07 The conservation of the human and mouse promoter regions is over 70% (Grillot et al., 1997). Like the human bcl-x promoter, the murine bcl-x promoter also contains a high concentration of sites (11 EBS in

1995). Bcl-xL expression has been shown to be activated by retroviral insertions in murine myeloid and T cell hematopoietic malignancies demonstrating that the expression of Bcl-xL can also be altered in cancer (Packham et al., 1998).

The bcl-xL transcript is upregulated in hematopoietic cells upon a variety of stimuli. Among these are stimuli including interleukin-2 (IL-2), IL-3, IL-6, granulocyte macrophage colony stimulating factor (GM-CSF), colony stimulating factor (CSF-1), leukemia inhibitory factor (LIF), and erythropoietin (Epo) which induce the survival and/or proliferation of hematopoietic cells. bcl-x has been shown to be an immediate early gene in Epo-treated HCD57 erythroleukemia cells (Socolovsky et al., 1999) whereas in myeloid cells, bcl-x was shown to be a delayed early gene whose transcriptional activation is dependent on de novo protein synthesis after CSF-1 (Sevilla et al., 1999) or IL-3 (Packham et al., 1998) stimulation. In addition to the bcl-xL transcript having a relatively short half life (Sevilla et al., 1999), the expression of the Bcl-xL protein parallels that of the bcl-xL transcript (Packham et al., 1998). It was therefore important to clone and characterize the bcl-x promoter to gain insight as to how bcl-x is regulated at the transcriptional level upon these different cytokine or growth factor signals.

The human and murine bcl-x promoters have been isolated and two distinct regions of the mouse bcl-x gene have been shown to have promoter activity (Grillot et al., 1997). The first promoter region of 57 bp is found immediately upstream of the first coding exon (exon II) and the second promoter region is upstream of the first non-coding exon (exon I). Major transcription initiation sites have been mapped to both regions. The differences in promoter usage may be attributed to a specific cell type or to the status of differentiation of the cell, although this remains to be determined. Sequence comparisons between the human and mouse promoters permitted the identification of highly conserved consensus binding sites for different transcription factors which have been shown to activate the bcl-x promoter.

Ets

The Ets family of transcription factors consists of approximately 30 members all possessing a conserved DNA binding domain of about 85 amino acids known as the "E" or "Ets" domain (Boulukos et al., 1989; reviewed in (Ghysdael and Bourex, 1997)). Ets1, the progenitor to v-Ets found in the E26 retrovirus, and Ets2 are 97% conserved in the Ets domain (Boulukos et al., 1988), whereas PU.1/Sp1.1 is highly divergent in this domain [37% identity; (Wasylyk et al., 1993)]. These differences in sequence identity of the Ets domain allow Ets1, Ets2 and PU.1/Sp1.1 to bind to common as well as distinct optimal DNA target sequences known as Ets binding sites (EBS).
700 bp). Ets2, but also Ets1 and more distantly related PU.1, all individually transcriptionally activate the bcl-x promoter with similar capacities (Sevilla et al., 1999). Deletions of distal sites show that maximal activity requires the integrity of these sites (Sevilla et al., 1999). Together, these results show that different members of the ets family play a role in inhibiting programmed cell death and at least one mechanism of inhibition by Ets transcription factors is by regulation of expression of the bcl-x gene.

Rel/NFκB

Rel/NF-κB transcription factors are homo- and heterodimeric proteins consisting of related subunits. Rel/NF-κB transcription factors rapidly translocate to the nucleus upon growth factor, cytokine, viral or stress stimuli and regulate the expression of many genes important for the function of the immune system (Hatada et al., 2000). Members include p50 (NFκB1), p52 (NFκB2), p65 (RelA), c-Rel, the progenitor to v-Rel of the Rev-T avian retrovirus, and RelB (for review see MacKichan and Israel, 1997). Gene disruption studies in mice have demonstrated that Rel/NFκB transcription factors are critical in regulating genes induced during immune responses (see Grossmann et al., 1999). Several in vivo studies suggested that Rel/NFκB played a role in the inhibition of apoptosis since inactivation of RelA/p65 in relA-/ mice leads to embryonic death due to massive apoptosis of the liver (Beg et al., 1995). Double knock-out c-rel-/relA-/ mice die earlier in utero than relA-/ from increased apoptosis of the liver, and hematopoietic progenitors recovered from c-rel-/relA-/ fetal livers fail to support survival of lethally irradiated mice (Grossmann et al., 1999). These results demonstrate that both c-Rel and RelA have overlapping functions and regulate the survival of committed hematopoietic progenitors.

Many genes implicated in inducing or inhibiting apoptosis contain NFκB-like elements in their promoter regions [see Tables in (Dixon et al., 1997; Chen et al., 1999)]. Four recent studies show that Rel/NFκB is important in the regulation of Bcl-xL expression in cells. Tax, a regulatory protein encoded by the human T-cell leukemia virus type 1, renders the CTLL-2 mouse T cell line IL-2-independent (Iwanaga et al., 1999). This first study showed that the loss of IL-2 dependence and resistance to apoptosis of these cells correlate with an increase of Bcl-xL expression induced by Tax through a NFκB pathway (Tsukahara et al., 1999). CD40, a member of the tumor necrosis factor receptor family, induces survival of B cells. In another study, Lee et al., showed that NFκB upregulated Bcl-xL expression and that this upregulation is required for CD40 survival signals in human Daudi and Ramos B cell lines (Lee et al., 1999). In other studies, using human HT1081 fibrosarcoma cells and HeLa cells expressing inducible Rel proteins, Chen et al., showed that both c-Rel and RelA/p65 increase Bcl-xL expression (Chen et al., 2000). Finally, macrophages from p50-/ mice have increased Bcl-xL levels and are more resistant to silica-induced cell death (Chen et al., 1999). Silica was shown to activate p50/p50 NFκB1 homodimers in macrophages obtained from wildtype mice and to induce apoptosis, whereas silica activates p65-containing complexes in macrophages from p50-/ mice (Chen et al., 1999).

Two NFκB-like sites are found in the 700 bp bcl-x promoter sequence (Fig. 1). Although p65/RelA, p50/NFκB1, RelB and c-Rel all bind to these NFκB-like elements (Chen et al., 1999, 2000; Lee et al., 1999; Tsukahara et al., 1999), only c-Rel and p65 were shown to transactivate the bcl-x promoter in hematopoietic cells (Chen et al., 1999; Lee et al., 1999; Chen et al., 2000).

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Fig. 1. The structure of the 5' regulatory sequences of the human bcl-x gene. Binding sites for Ets, Rel/NFκB, STAT and AP-1 transcription factor families were determined using the MatInspector program (Quandt et al., 1995). Conserved consensus motifs, TATA box, exons, and a major transcription initiation site (+1) are indicated in the figure.
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These results show that Rel/NFκB, another important transcription factor family, plays a role in the regulation of bcl-x expression specifically in B and T cells. Rel/NFκB can also function as a negative regulator of Bcl-xL in double-positive CD4+/CD8+ thymocytes (Hettmann et al., 1999). Therefore, additional experiments are needed to clarify under what conditions Rel/NFκB functions as a positive regulator or as a negative regulator of bcl-x expression.

STATs

Signal Transducers and Activators of Transcription (STATs) play key roles in growth factor, cytokine or hormone-mediated intracellular signal transduction. Ligand binding initiates phosphorylation of tyrosine residues and subsequent homo- or heterodimerization of the STAT proteins. This phosphorylation activates STATs to migrate from the cytoplasm into the nucleus, to bind to specific DNA sequences in the promoter regions of certain genes and to activate or repress the transcription of these target genes. Seven members of the STAT family as well as four isoforms lacking their variable transactivation domains have been identified.

It was first reported that Bcl-xL proteins are regulated by the Jak kinase pathway independent of STATs in hematopoietic cells (Puckham et al., 1998). This conclusion was based on experiments using the mouse immortalized myeloid progenitor 32D-3 cell line expressing different EpoR mutants treated with Epo. However, more recent studies from several laboratories indicate that STATs do effect Bcl-xL expression. Embryos from sta5a-/- sta5b-/- double knockout mice show severe defects in fetal liver erythroid progenitors and that these erythroid progenitors undergo increased apoptosis in vitro (Socolovsky et al., 1999), sta5a-/- sta5b-/- erythroid progenitors are less responsive to Epo (Socolovsky et al., 1999), a cytokine essential for their growth and survival, and Epo activation of STAT5 in Epo-dependent HCD57 erythroleukemia cells mediates the induction of Bcl-xL through direct binding of STAT5 to the bcl-x promoter (Silva et al., 1999). Only STAT5, and not STAT1 or STAT3, bind to the bcl-x promoter in response to Epo in these cells (Silva et al., 1999).

The regulation of bcl-x transcription by STAT5 is not limited to erythroid cells. The mouse pro-B Ba/F3 cell line is dependent on IL-3 for its growth and survival. Bcl-xL mRNA expression is upregulated (Nosaka et al., 1999). A complementary approach using a "dominant negative" mutant of STAT5a in Ba/F3 cells showed that Bcl-xL was downregulated and IL-3 removal rendered these cells more sensitive to apoptosis (Dumon et al., 1999). These authors went further to demonstrate that STAT5 transcriptionally activated the bcl-x promoter in Ba/F3 cells (Dumon et al., 1999).

Other members of the STAT family may be implicated in the transcriptional regulation of the bcl-x gene and this regulation may occur in nonhematopoietic cell types as well. Supporting this notion are studies showing that STAT1, but not STAT3, mediates the expression of the bcl-x gene upon LIF treatment of cardiac myoblasts (Fujio et al., 1997).

AP1 complexes

c-Fos and c-Jun, the progenitors of their oncogenic counterparts in murine osteosarcoma viruses FBJ.MuSV and FBR.MuSV, and in a chicken osteosarcoma ASV17, respectively, are immediate early genes which are rapidly activated in response to a wide variety of extracellular stimuli. The fos family consists of c-Fos, Fra-1, Fra-2 and FosB and the jun family consists of c-Jun, JunB and JunD. Both Fos and Jun are members of the basic/leucine zipper family. Jun proteins can form homodimers but Fos proteins cannot homodimerize. However, Fos proteins can heterodimerize with Jun proteins and regulate the transcription of target genes whose promoters contain AP1 DNA binding sites. Jun homodimers or Fos/Jun heterodimers are also known as the AP1 complex. Although the expression of Fos and Jun members is often transient, their API activity have been shown to profoundly effect both proliferation and differentiation pathways [for review see (Bannister and Kouzarides, 1997)].

More recently, API activity has been implicated as being potentially important in regulating anti-apoptotic genes (Jacobs-Helber et al., 1998). When c-Jun was present in the API complex of Epo-treated HCD57 erythroid cells, these cells survived. However, Epo withdrawal led to the presence of JunB in the API complex and JunB activity correlated with increased death. A dominant negative mutant of c-Jun inhibited the downregulation of Bcl-xL expression and rendered HCD57 cells resistant to cell death after Epo depletion (Jacobs-Helber et al., 1998). Characterization of the bcl-x promoter revealed the presence of an API site upstream of the first non-coding exon (Fig. 1) and that c-Fos and c-Jun were shown to transactivate the bcl-x gene via this API site (Sevilla et al., 1999).

Cooperation of different transcription factor families in regulating bcl-x gene expression

The activation of Ets, Rel/NF-κB, STATs and API-1 transcription factors after stimulation with a variety of extracellular signalling molecules in different hematopoietic lineages clearly correlates with the increased expression of Bcl-x. Since members of these different families are rapidly activated upon many of the same stimuli and in the same cell types, several questions remain: is there cooperation between the different classes of transcription factors in bcl-x gene regulation and if so, what are these factors and under which conditions do they cooperate? To begin to address these questions, recent studies from our laboratory have investigated the effects on the coexpression of members
of the different transcription factor families on \textit{bcl-x} regulation.

The protein of reference in these studies was Ets2. When STAT5α was activated in the presence of Ets2, STAT5 actually diminished the capacity of Ets2 to transactivate (Sevilla et al., 2001). Either STAT5α was physically interfering with the capacity of Ets2 to bind to EBS, or STAT5α was sequestering an unidentified cofactor from Ets2. A potential cofactor may be a protein of the p300/CBP-family (CBP) family which interacts with both STAT5 (Pfitzner et al., 1998) and Ets2 (Jayaraman et al., 1999) (see below).

Coexpression of c-Fos and c-Jun with Ets2, resulted in an increase in transactivation, but this effect was only additive (Sevilla et al., 2001). Many promoters contain AP-1/Ets binding sites and cooperation between the AP1 complex and Ets is well documented [for review see (Bannister and Kouzarides, 1997) and references therein]. The basic region of c-Jun has been shown to physically interact with the DNA binding domain of several members of the \textit{ets} family including Ets1, Ets2 and PU.1 (Bassuk and Leiden, 1995; Basuayux et al., 1997). Yet the significance of AP1/Ets activity on the \textit{bcl-x} promoter needs further attention.

Rel/NF-kB and c-Fos and c-Jun are often activated in parallel in the same cell type upon the same stimulus. For example, as seen in this review Rel/NF-kB and c-Fos and c-Jun are all activated in Epo-treated HCD57 cells. It appears that via their leucine zippers, c-Fos/c-Jun interact with the rel homology domain of Rel/NF-kB and stimulate Rel/NF-kB DNA binding (Stein et al., 1993). Rel/NF-kB members have also been shown to collaborate with AP1 and Ets on the GM-CSF promoter in human Jurkat T cells (Thomas et al., 1997). Whether these interactions occur or not on the \textit{bcl-x} promoter after Epo stimulation of erythroid cells or after stimulation of other cell types has not yet been established.

Surprisingly, coexpression of two members of the \textit{ets} family, PU.1 and Ets2, resulted in a clear synergy on the \textit{bcl-x} promoter (Sevilla et al., 2001). This synergy of Ets2 and PU.1 was specific since coexpression of Ets1 with either Ets2 or with PU.1 had no effect on \textit{bcl-x} activity. Since Ets1 is not expressed in macrophages, whereas Ets2 and PU.1 proteins are, the regulation of the \textit{bcl-x} promoter at the molecular level parallels biological expression. Both PU.1 and Ets2 transactivation domains are required for this synergy and the integrity of the \textit{bcl-x} promoter is necessary for maximal synergy between Ets2 and PU.1 since deletions of 2 or more sites greatly reduced the synergistic capacity of these two transcription factors. Interestingly, PU.1 and Ets2 proteins are known to bind to DNA as monomers [reviewed in (Ghysdael and Bourieux, 1997)] and do not physically interact (personal observations). Either these proteins do not directly interact or their interactions are weak and/or transient. It is possible that these proteins interact via a third bridging factor. Proteins of the p300/CBP family are coactivators of transcription binding to transcription factors and affecting their transcriptional capacities, and are known to have histone acetyltransferase functions capable of modulating chromatin structure. Recently, p300/CBP have been identified as proteins interacting with PU.1 (Yamamoto et al., 1999) or Ets2 (Jayaraman et al., 1999). Preliminary experiments suggest that PU.1, Ets2 and p300/CBP physically interact and cotransfections of HeLa cells with p300/CBP greatly increased the activities of Ets2 and PU.1 on the \textit{bcl-x} promoter. Therefore p300/CBP appears to be a ternary factor involved in Ets2/PU.1 synergistic activity on the \textit{bcl-x} promoter (Zaldumide et al, in prep.).

Conclusions

The Bcl-x\textsubscript{L} protein plays an important role in maintaining the integrity of mitochondria thereby inhibiting the release of factors which activate the pro-apoptotic caspase cascade. The level of protein expression parallels that of its mRNA transcript and it is well established that high Bcl-x\textsubscript{L} expression correlates with high cell survival in cells subjected to apoptotic signals. \textit{bcl-x} is regulated at the transcriptional level upon activation of cells with a variety of stimuli including survival/growth factors. Recent studies from several laboratories have characterized several transcription factor families involved in regulating the \textit{bcl-x} gene. Members of the Ets, Rel/NF-kB, STAT and AP-1 families of transcription factors have all been implicated in this regulation in hematopoietic cells. Although some of these transcription factor families activate \textit{bcl-x} transcription in an additive or synergistic fashion, further studies will be needed to determine under which circumstances and in what cell types these transcription factors function together to regulate \textit{bcl-x} gene expression.

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