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Review:

DNA-damage response network at the crossroads of cell-cycle checkpoints, cellular senescence and apoptosis*

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Abstract: Tissue homeostasis requires a carefully-orchestrated balance between cell proliferation, cellular senescence and cell death. Cells proliferate through a cell cycle that is tightly regulated by cyclin-dependent kinase activities. Cellular senescence is a safeguard program limiting the proliferative competence of cells in living organisms. Apoptosis eliminates unwanted cells by the coordinated activity of gene products that regulate and effect cell death. The intimate link between the cell cycle, cellular senescence, apoptosis regulation, cancer development and tumor responses to cancer treatment has become eminently apparent. Extensive research on tumor suppressor genes, oncogenes, the cell cycle and apoptosis regulatory genes has revealed how the DNA damage-sensing and -signaling pathways, referred to as the DNA-damage response network, are tied to cell proliferation, cell-cycle arrest, cellular senescence and apoptosis. DNA-damage responses are complex, involving "sensor" proteins that sense the damage, and transmit signals to "transducer" proteins, which, in turn, convey the signals to numerous "effector" proteins implicated in specific cellular pathways, including DNA repair mechanisms, cell-cycle checkpoints, cellular senescence and apoptosis. The Bcl-2 family of proteins stands among the most crucial regulators of apoptosis and performs vital functions in deciding whether a cell will live or die after cancer chemotherapy and irradiation. In addition, several studies have now revealed that members of the Bcl-2 family also interface with the cell cycle, DNA repair/recombination and cellular senescence, effects that are generally distinct from their function in apoptosis. In this review, we report progress in understanding the molecular networks that regulate cell-cycle checkpoints, cellular senescence and apoptosis after DNA damage, and discuss the influence of some Bcl-2 family members on cell-cycle checkpoint regulation.

Key words: DNA-damage response network, Cell cycle, Cellular senescence, Apoptosis, Bcl-2 family
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INTRODUCTION

The DNA-damage response network is highly complex and involves a multitude of proteins that sense the damage, transduce signals into cells and execute cellular responses. DNA double-strand break "sensor" proteins constitute NBS1/Mre11/Rad50 multiprotein complexes recruited at DNA damage sites, where they create rapidly-expanding nuclear foci referred to as DNA damage heterochromatin foci, with phosphorylated histone γ-H2AX and other proteins, including BRCA1, 53BP1 and MDC1. The "transducer" protein of DNA double-strand breaks is the phosphoinositide 3-kinase-related kinase ATM, which, in turn, activates multiple "effector" proteins, including p53, Mdm2, and CHK2. DNA-PK, another phosphoinositide 3-kinase-related kinase recruited at DNA damage heterochromatin foci, is involved in the non-homologous end-joining repair pathway, whereas Rad51 is implicated in DNA recombination repair pathways. Although less well-characterized, DNA replication fork stalling and DNA single-strand break

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alarms include ATR, ATRIP, RPA, Rad9/Rad1/Hus1, Rad17/RSR and claspin. ATR, a phosphoinositide 3-kinase-related kinase, in turn, activates multiple "effector" proteins, including p53 and CHK1 (reviewed in Bakkenist and Kastan, 2004; Shiloh, 2006). Activation of these "effector" proteins influences cell-cycle progression and arrest, cellular senescence and apoptosis activation.

CELL-CYCLE CHECKPOINT REGULATION

Timely progression through the cell division cycle ensures the correct transmission of genetic information from a cell to its daughters. Once stimulated in proper environment with suitable growth factors, quiescent cells leave a resting phase of the cell cycle, called gap 0 (G0), and enter the gap 1 (G1) phase, prior to the DNA replication or synthesis (S) phase, followed by a second gap (G2) phase, and cell division or mitosis (M). Cell-cycle checkpoints maintain the order and fidelity of cell-cycle events in response to replicative stress and DNA strand breaks (Nigg, 2001). The molecular mechanisms associated with these cell-cycle checkpoints entail the transient inactivation of a series of specific cyclin-dependent kinases (cdks) and their respective regulatory cyclin subunits. During normal phase progression and at key cell-cycle transition phases, specific cdk-cyclin complexes are activated by dephosphorylation, mediated by the dual specificity cdc25 phosphatase family, including cdc25A, -B and -C. The cdk-cyclin complexes influencing G1 progression and G1/S cell-cycle checkpoint are primarily cdk4-cyclinD, cdk6-cyclinD and cdk2-cyclinE (Koff *et al*., 1992; Sherr and Roberts, 1995). In response to DNA damage, ATM/ATR protein kinases activate the checkpoint serine/threonine kinases, CHK1 and CHK2. To prevent entry into S phase, CHK1 and CHK2 target the cell-cycle regulatory phosphatase cdc25A. Phosphorylation of cdc25A on several residues, including Ser123, leads to its ubiquitin-mediated proteolysis, and to sustained phosphorylation and inhibition of cdk2-cyclinE complexes, that normally promote G1/S transition (Falck *et al*., 2001). Several small proteins, the cdk-cyclin inhibitors (cdkIs), which bind to and inhibit cdk-cyclin activities, also play critical role in the G1/S cell-cycle checkpoint. The most potent cdkIs are p21, p27 and p57 for cdk2-cyclinE, and p16 for cdk4-cyclinD or cdk6-cyclinD (Sherr and Roberts, 1995). Activation of these cdkIs causes G1/S cell-cycle arrest after DNA damage (Kohn *et al*., 1994; Hunter and Pines, 1994; Kastan *et al*., 1995; Kohn, 1996; Kaufmann and Paules, 1996; Jacks, 1996; Tanaka *et al*., 1996). Indeed, ATM/ATR and CHK1/CHK2 kinases also target p53. In turn, p53 phosphorylation and stabilization by ATM/ATR and CHK1/CHK2 lead to accumulation of the cdkI p21, which is involved in more sustained G1/S cell-cycle arrest (Shiloh, 2001).

Progression into the S phase and transition from G2 into M are regulated by the serine-threonine cdk2 and cdk1 (cdc2), respectively. Activation of cdk2 and cdk1 (cdc2) requires the association of their positive subunits, cyclinA and cyclinB, respectively, and the phosphorylation of Thr161 by cdk-activating kinase. These cdk-cyclin complexes are also negatively regulated by phosphorylation at Thr14 and Tyr15, which are catalyzed by inhibitory protein kinases, including Wee1, Myt1 and Mik1 (Nigg, 2001; Draetta and Beach, 1988; Draetta *et al*., 1989; Riabowol *et al*., 1989; Ducommun *et al*., 1991; King *et al*., 1994; Labib *et al*., 1995; McGowan and Russell, 1995; Mueller *et al*., 1995; Liu *et al*., 1997; O'Connell *et al*., 1997; Booher *et al*., 1997). During S phase progression and at G2/M phase transition, dephosphorylation of Thr14 and Tyr15 by the cdc25 protein phosphatase cdc25A, -B, and -C, triggers cdk2-cyclinA (intra-S phase) and cdk1 (cdc2)-cyclinB (at G2/M) activation. During the DNA-damage response, activation of ATM/ATR and the downstream checkpoint kinases CHK1/CHK2 leads to the phosphorylation of all 3 cdc25 phosphatases, which creates binding sites for 14-3-3 proteins and sequestration of the phosphatases away from cdk2-cyclinA and cdk1 (cdc2)-cyclinB (Borgne and Meijer, 1996; Peng *et al*., 1997; Zeng *et al*., 1998; Sanchez *et al*., 1997; Matsuoka *et al*., 1998; Brown *et al*., 1999; Liu *et al*., 2000; Furnari *et al*., 1999; 1997; Lammer *et al*., 1998; Hofmann *et al*., 1998; Aguda, 1999; Schmitt *et al*., 2006). These molecular events provoke S-phase slowing and G2/M cell-cycle arrest. The importance of p53 in the intra-S phase and G2/M checkpoints is uncertain because most cells lacking p53 retain the ability to slow S-phase progression and to arrest at G2/M after DNA damage (O'Connor *et al*., 1997; O'Connor, 1997;

Gupta *et al*., 1997; Passalaris *et al*., 1999; Cliby *et al*., 2002; Flatten *et al*., 2005). However, studies have indicated that p53 attenuates the activity of cyclinB1 promoter or promotes the transcriptional activation of the sequestering protein 14-3-3 (Hermeking *et al*., 1997; Innocente *et al*., 1999). Others reported that the p53-regulated GADD45 protein associates with and inhibits cdk1 (cdc2)-cyclinB kinase activity in response to DNA damage (Wang *et al*., 1999a; Zhan *et al*., 1999). Additional regulators of the G2/M checkpoint are the mitotic serine/threonine Polo-like (PLK) and Aurora-like kinases. PLK1 promotes mitotic entry by phosphorylating and activating cdc25C, and in response to DNA damage, PLK1 is inhibited by an ATM-dependent mechanism. Unlike PLK1, PLK3 is involved in the G2/M arrest by phosphorylating and inhibiting cdc25C (Smits *et al*., 2000; van Vugt *et al*., 2001; Xie *et al*., 2001). AuroraA kinase is normally required for recruitment and activation of cdk1 (cdc2)/cyclinB and commitment of cells into M (Hirota *et al*., 2003). In response to DNA damage, inhibition of AuroraA kinase is associated to activation of G2/M checkpoint, whereas its overexpression results in checkpoint bypass (Cazales *et al*., 2005; Marumoto *et al*., 2002).

Although these pathways leading to cell-cycle delay have been identified during the past few years, the dynamic spatio-temporal coordination and regulation of the DNA-damage response network remain poorly understood. Today, a new challenge in cell-cycle checkpoint biology is to understand how cell-cycle checkpoint pathways are coordinated and organized in space and time, to trigger cellular response to DNA damage (Lukas *et al*., 2004).

CELLULAR SENESCENCE

Recent investigations in the field of cellular senescence have revealed the importance of DNA-damage responses and cell-cycle checkpoints to initiate cell-cycle arrest associated with cellular senescence. Replicative (or the Hayflick limit) and premature senescence share a common signal, now recognized as DNA strand breaks. In replicative senescence, telomere erosion and shortening yield DNA double-strand breaks at chromosome ends that initiate DNA damage responses (Herbig *et al*., 2004; d'Adda di Fagagna *et al*., 2003). In premature senescence, oncogenic activation leads to elevated intracellular levels of reactive species, augmented numbers of active replicons, alterations in DNA replication fork progression, and the appearance of DNA single- and double-strand breaks that initiate DNA-damage responses (Takahashi *et al*., 2006; Di Micco *et al*., 2006; Bartkova *et al*., 2006; Mallette *et al*., 2007; Hemann and Narita, 2007). Similarly, DNA-damaging chemotherapeutic and radiotherapeutic agents provoke DNA replication fork stalling and/or DNA single- and double-strand breaks with activation of the DNA-damage response network (Holliday and Tarrant, 1972; Kung *et al*., 1990; Di Leonardo *et al*., 1994; Waldman *et al*., 1996; Robles and Adami, 1998; Chang *et al*., 1999a; 1999b; Suzuki *et al*., 2001a; Campisi, 2001; Johnstone *et al*., 2002; Schmitt *et al*., 2002; Han *et al*., 2002; Lee and Schmitt, 2003). Indeed, in models of cellular senescence, ATM/ATR mediate the activation of cell-cycle checkpoints associated with cellular senescence, mainly via p53, CHK1 and CHK2, with the participation of p21, p16 and Rb (reviewed in Schmitt, 2007). It has been suggested previously that after genotoxic drug treatment, cell-cycle arrest and senescence development are dependent on the p53/p21 pathway in HCT116 colon cancer cells (Han *et al*., 2002). Similar observations concerning the importance of the p53/p21 pathway have been reported with other chemotherapeutic agents or irradiation (Di Leonardo *et al*., 1994; Waldman *et al*., 1996; Bunz *et al*., 1998; Linke *et al*., 1997). Likewise, studies with bleomycin, actinomycin D and cyclophosphamide have revealed that cells respond to these agents by engaging a p53/p16-dependent long-term senescence program (Robles and Adami, 1998; Schmitt *et al*., 2002). However, others have reported senescence phenotypes in p53-mutated cell lines derived from various types of human solid tumors, including cervical, larynx and colon carcinoma, glioma, osteosarcoma (Chang *et al*., 1999a) and lymphoma cell lines (Schmitt *et al*., 2007). Typically, senescent cells are observed by flow cytometry after DNA staining as broader G1 or G2/M peaks, and with the appearance of a senescence-associated β-galactosidase activity (pH 6.0).

The DNA-damage responses induced in the early phase of cellular senescence initiation explain how cells will activate cell-cycle checkpoints and

undergo cell-cycle arrest at specific phases of the cell cycle. However, after DNA damage, cell-cycle arrests do not always lead to cellular senescence. Indeed, cell-cycle arrests often afford cells the opportunity to repair DNA damage before progressing to the next phase of the cycle. In turn, inappropriate progression of damaged cells through the cell cycle is often associated with mitotic catastrophe, apoptosis and cell death. Thus, the stabilization of cell-cycle arrests to irreversible senescence involves other yet unknown critical events. Recently, epigenetic changes, including histone H3 lysine K9 trimethylation (H3K9) associated with gene silencing, have been suggested as critical mechanisms associated with the stabilization of cell-cycle arrest to cellular senescence, as senescent cells show focal histone H3K9 trimethylation. These foci are now referred to as senescence-associated heterochromatin foci (SAHF) (Schmitt, 2007; Strunnikova *et al*., 2005; Guney and Sedivy, 2006; Zhang *et al*., 2007). Early evidence indicated that H3K9 trimethylation controls DNA methylation in several model organisms (Tamaru and Selker, 2001; Tamaru *et al*., 2003; Jackson *et al*., 2002). Methylation of CpG islands in promoters and locus control regions is strongly associated with H3K9 trimethylation and gene silencing. Indeed, others have indicated that some gene promoters are hypomethylated, whereas others undergo hypermethylation during cellular senescence, suggesting that differential DNA methylation patterns at specific gene promoters and locus control regions may stabilize the senescence phenotype (Tollefsbol and Andrews, 1993; Machwe *et al*., 2000; Kang *et al*., 2001; Neumeister *et al*., 2002; Lopatina *et al*., 2002; Sun and Arceci, 2005).

BCL-2 FAMILY MEMBERS AND APOPTOSIS

The Bcl-2 gene was first identified at the chromosomal breakpoint of t(14:18)-bearing B cell lymphomas (Tsujimoto *et al*., 1984; Cleary *et al*., 1986), and was unexpectedly found to act as a new class of oncogenes that function to prevent apoptosis instead of directly promoting cellular proliferation (Hockenbery *et al*., 1990; Korsmeyer, 1992; McDonnell *et al*., 1993; Vaux *et al*., 1988). Bcl-2 is the founder of a large family of apoptosis regulators that either promote cell survival or facilitate cell death. The pro-survival members are multidomain proteins that contain BH1, BH2 and BH3 (A1/Bfl-1), BH2 and BH4 (Bcl-xES), and those most similar to Bcl-2 have all 4 BH domains (Bcl-2, Bcl-xL, Mcl-1, Bcl-w, Brag-1, Boo/Diva, Bcl-B/Bcl-2L-10) (Cleary *et al*., 1986; Boise *et al*., 1993; Choi *et al*., 1995; Das *et al*., 1996; Gibson *et al*., 1996; Inohara *et al*., 1998a; Ke *et al*., 2001; Kozopas *et al*., 1993; Lin *et al*., 1993; Schmitt *et al*., 2004; Song *et al*., 1999; Zhang *et al*., 2001). According to their structure and biochemical function, the pro-apoptotic members can be further divided into 2 subgroups: multidomain proteins composed of BH domains 1 to 3 (Bax, Bak, Bok/Mtd, Bcl-rambo), BH2 and BH3 (Bcl-gL) or BH4 and BH3 (Bcl-xS) (Boise *et al*., 1993; Chittenden *et al*., 1995a; Farrow *et al*., 1995; Guo *et al*., 2001; Hsu *et al*., 1997a; Inohara *et al*., 1998b; Kataoka *et al*., 2001; Kiefer *et al*., 1995; Oltvai *et al*., 1993), and BH3-only proteins built of 1 or 2 BH3 domains (Bad, Bid, Bik/Nbk/Blk, Bim/Bod, Hrk/Dp5, Bnip1, Bnip3, Nix, Puma/Bbc3, Noxa, Bcl-gS, Mcl-1s, Map1, Bmf, Spike and ApoL6) (Guo *et al*., 2001; Bae *et al*., 2000; Bingle *et al*., 2000; Boyd *et al*., 1994; 1995; Chen *et al*., 1999; Han *et al*., 1996; 2001; Hegde *et al*., 1998; Hsu *et al*., 1998; Imaizumi *et al*., 1999; Inohara *et al*., 1997; Matsushima *et al*., 1998; Nakano and Vousden, 2001; O'Connor *et al*., 1998; Oda *et al*., 2000; Puthalakath *et al*., 2001; Tan *et al*., 2001; Wang *et al*., 1996; Yang *et al*., 1995; Yasuda *et al*., 1999; Yu *et al*., 2001; Liu *et al*., 2005). In addition to the BH domains, some proteins contain a flexible loop, a pore-forming domain and a transmembrane domain at the carboxy terminal extremity (Adams and Cory, 2001; Chao and Korsmeyer, 1998; Reed, 1997; 1998; Vander Heiden and Thompson, 1999; Zamzami *et al*., 1998; Cory and Adams, 2002).

The various Bcl-2 homologues function, at least in part, through protein-protein interactions, forming a complex dynamic network of homo- and heterooligomers, depending on the cellular environment and their subcellular localization. Mutagenesis experiments have suggested that the dimerization potential of Bcl-2-like proteins is greatly influenced by their specific combination of BH domains (Chittenden *et al*., 1995b; Kelekar and Thompson, 1998; Yin *et al*., 1994). Thus, elucidation of the 3-dimensional structure of the anti-apoptotic Bcl-xL has provided a first model in which the α helices located in the BH1, BH2

and BH3 domains create an elongated hydrophobic pocket where a BH3 amphipathic α helice of another Bcl-2-like protein can bind, analogously to a peptide ligand binding to its receptor (Muchmore *et al*., 1996; Diaz *et al*., 1997; Sattler *et al*., 1997). Heterodimerization between pro- and anti-apoptotic molecules may neutralize one another's activity, suggesting that the relative concentration of one faction versus the other greatly influences the susceptibility of cells to a death signal (Oltvai *et al*., 1993; Sedlak *et al*., 1995). Because it provides binding ability, the BH3 motif has become a potent mediator of cell death and is often uniquely required for cell-killing activity (Chittenden *et al*., 1995b; Polster *et al*., 2001). Two distinct models have been proposed to explain the killing activity of the BH3-only proteins (reviewed in Adams and Cory, 2007). The direct activation model proposes that after a death stimuli, BH3-only proteins promote apoptosis by binding to and inhibiting pro-survival molecules, like Bcl-2, Bcl-xL Bcl-w, Mcl-1 and A1, or by binding to other death agonists, like the multidomain Bax and Bak proteins, which become activated and exert their pro-apoptotic activities at the mitochondrial level. BH3-only proteins that neutralize pro-survival proteins are referred to as BH3 "enabler or sensitizing" proteins, while those that bind pro-apoptotic Bax or Bak are called BH3 "activator or activating" proteins (Chittenden, 2002; Letai *et al*., 2002; Kuwana *et al*., 2005; Kim *et al*., 2006). The indirect activation model suggests that all BH3-only proteins engage only the pro-survival proteins and act by preventing them from inhibiting Bax or Bak activation (Chen *et al*., 2005; Willis *et al*., 2005; 2007).

The p53-mediated pathways have been explored extensively in the context of tumor suppression and their response to DNA-damaging agents (Kohn *et al*., 1994; Hunter and Pines, 1994; Kastan *et al*., 1995; Kohn, 1996; Kaufmann and Paules, 1996; Jacks, 1996; Tanaka *et al*., 1996; O'Connor *et al*., 1997; O'Connor, 1997; Gupta *et al*., 1997; Passalaris *et al*., 1999; Hermeking *et al*., 1997; Innocente *et al*., 1999; Wang *et al*., 1999a; Zhan *et al*., 1999; Johnstone *et al*., 2002; Levine, 1997; Lowe *et al*., 1993; 1994; Gottlieb and Oren, 1998). At the level of transcription, multiple p53 target genes, including those of the Bcl-2 family, play crucial roles in promoting apoptosis induced by genotoxic agents. Among them, the Bax gene was one of the first p53-dependent apoptotic targets to be identified (Miyashita and Reed, 1995; Miyashita *et al*., 1994); then, other members of the Bcl-2 family were reported to be p53-downstream targets, such as the BH3-only members Bid (Sax *et al*., 2002), Puma (Nakano and Vousden, 2001; Yu *et al*., 2001; Villunger *et al*., 2003) and Noxa (Oda *et al*., 2000; Shibue *et al*., 2003). More recently, others have revealed that p53 itself targets mitochondria, where it associates with and activates the multidomain pro-apoptotic Bax and Bak at the protein level (Chipuk *et al*., 2004; Leu *et al*., 2004; Perfettini *et al*., 2004; Mihara *et al*., 2003; Dumont *et al*., 2003; Chipuk *et al*., 2005).

Much less is known about the effector genes involved in p53-independent responses after DNA damage. However, most human tumors lose the expression of a functional p53, and they likely represent difficult targets in cancer therapies. Paradoxically, several observations have disclosed that cells lacking the ability to transduce a cell-cycle checkpoint, as a consequence of targeted disruption of p53 or mutated p53, could display hypersensitivity to DNA-damaging treatments, including DNA topoisomerase I and II inhibitors, and undergo apoptosis (Gupta *et al*., 1997; Waldman *et al*., 1996; Kaufmann, 1989; 1998; Slichenmyer *et al*., 1993; Thomas *et al*., 1996; Bertrand *et al*., 1991; 1993; Solary *et al*., 1992; Dubrez *et al*., 1995; 1996; Shimizu and Pommier, 1997; Kaufmann and Earnshaw, 2000; Droin *et al*., 1998).

p73 and p63, other p53 family members that can be activated when cells are damaged, also contribute to programmed cell death induction, in the presence or absence of p53 after DNA damage (Jost *et al*., 1997; Yang *et al*., 1998; Yuan *et al*., 1999; Gong *et al*., 1999; Agami *et al*., 1999; Costanzo *et al*., 2002; Flores *et al*., 2002; Bergamaschi *et al*., 2003; Freebern *et al*., 2003; Nozell *et al*., 2003). While the p73 and p63 functional domains necessary for mediating apoptosis have been characterized, much less is known about the p73 or p63 target genes of Bcl-2 family members (Jost *et al*., 1997; Yang *et al*., 1998; Yuan *et al*., 1999; Gong *et al*., 1999; Agami *et al*., 1999; Costanzo *et al*., 2002; Flores *et al*., 2002; Bergamaschi *et al*., 2003; Freebern *et al*., 2003; Nozell *et al*., 2003; Fontemaggi *et al*., 2002). Recently, Melino *et al*.(2004) reported that p73 isoform overexpression can directly induce Puma transactivation.

E2F1 transcription factor has been shown to

participate in the induction of apoptosis in the presence or absence of p53 (Hunt *et al*., 1997; Phillips *et al*., 1997; Holmberg *et al*., 1998). Overexpression of E2F1 itself can directly activate p73 transcription (Stiewe and Pützer, 2000) and regulate the expression of several genes involved in apoptosis, including the multi-domain pro-apoptotic Bak, the BH3-only proteins Bid, Bad, Bim, Noxa, Puma, Hrk, the adaptor protein Apaf-1 and caspase-3 and -7 (Muller *et al*., 2001; Stanelle *et al*., 2002; Pediconi *et al*., 2003; Hershko and Ginsberg, 2004). Some of these targeted genes are also regulated by E2F1 following cisplatin or doxorubicin treatment of p53-deficient mouse embryo fibroblasts (Hershko and Ginsberg, 2004), highlighting its importance for drug responses.

NFκB activation after DNA topoisomerase inhibitor treatment was shown to be p53-independent (Piret *et al*., 1999), but reported to be essential in p53-mediated cell death induced by DNA damage, highlighting its important role (Ryan *et al*., 2000). Activation of NFκB and c-Jun/Ap-1 contributes either to protect cells from death or activates cell death, depending on the cellular environment (Foo and Nolan, 1999; Mercurio and Manning, 1999; Grumont *et al*., 1998), and a growing number of genes related to apoptosis have been demonstrated to be induced by NFκB and c-Jun/Ap-1 in response to multiple stress-inducing agents, including DNA damage (Chu *et al*., 1997; Stehlik *et al*., 1998; Wang *et al*., 1998; 1999b; Tamatani *et al*., 1999; Zong *et al*., 1999; Stroka *et al*., 1999).

Bcl-2 family members generally localize to separate subcellular compartments in the absence of a death signal. Anti-apoptotic members, like Bcl-2 and Bcl-xL, usually reside on the cytoplasmic face of the outer mitochondrial membrane (OMM), endoplasmic reticulum and nuclear envelope (Hockenbery *et al*., 1990; Krajewski *et al*., 1993; Zamzami *et al*., 1996). In contrast, death-inducing members, such as Bax, Bad and Bid, are rather free in unstimulated cells, except for the multidomain Bak which seems to constitutively reside in the OMM (Gross *et al*., 1998; Korsmeyer *et al*., 2000; Hsu *et al*., 1997b). In turn, the BH3-only Bim and Bmf are linked to cytoskeleton components via binding to the large microtubular dynein motor complex and myosin V actin motor complex, respectively (Puthalakath *et al*., 1999; 2001). After a death signal, multidomain pro-apoptotic proteins, like Bax, undergo a conformational change which gives them the capacity to target and insert into intracellular membranes, especially in the mitochondria. The transmembrane domain appears to be important in conferring membrane-docking capacity to both pro- and anti-apoptotic members as well as in providing protein stability, even though reports indicate that deletion of this domain does not abrogate the function of most Bcl-2-like proteins (Borner *et al*., 1994; Nguyen *et al*., 1994).

Regulation of mitochondrial membrane permeabilization is the major means by which Bcl-2-like proteins exert their apoptosis regulatory effect. As a site of convergence for multiple death-inducing stimuli, the mitochondria are a pivotal decision centre that controls life and death by releasing apoptogenic factors in the cytosol. These death-inducing molecules are located within the mitochondrial intermembrane space and include cytochrome c (Kluck *et al*., 1997; Yang *et al*., 1997), DIABLO/Smac, a factor that promotes caspase activation by its effect on IAPs (inhibitor of apoptosis proteins) (Du *et al*., 2000; Verhagen *et al*., 2000), the nuclease activator AIF (apoptosis-inducing factor) (Susin *et al*., 1996; 1999a), Endo G (an apoptotic DNase) (Li *et al*., 2001; Parrish *et al*., 2001), HtrA2/Omni (an inhibitor of IAPs that also contains pro-apoptotic serine protease activity) (Suzuki *et al*., 2001b), and some pro-caspases (Krajewski *et al*., 1999; Mancini *et al*., 1998; Qin *et al*., 2001; Susin *et al*., 1999b). Permeabilization of the OMM is usually followed by caspase-9 activation and irreversible apoptosis. Bcl-2 family members may control the mitochondrial permeabilization phase (Desagher and Martinou, 2000) via 3 prevailing models: first, by forming autonomous channels in the OMM; second, by interfering with mitochondrial permeability transition pores (mPTP); and, finally, by promoting dynamic alterations in the structure of the lipid bilayer (Gross *et al*., 1998; Kluck *et al*., 1997; Yang *et al*., 1997; Antonsson *et al*., 1997; 2000; Minn *et al*., 1997; Chou *et al*., 1999; McDonnell *et al*., 1999; Schendel *et al*., 1998; Schlesinger *et al*., 1997; Bossy-Wetzel *et al*., 1998; Vander Heiden *et al*., 1997; Saito *et al*., 2000; Pavlov *et al*., 2001; Basañez *et al*., 1999; Kudla *et al*., 2000; Epand *et al*., 2002; Kuwana *et al*., 2002). Anti-apoptotic proteins seem to exert their function in part by inhibiting the formation of death-inducing pores by pro-apoptotic proteins, and a

study has reported that the Bcl-2 channel could potentially inhibit apoptosis by evoking H^+ efflux from the mitochondria, preserving mitochondrial transmembrane potential ($\Delta\Psi_m$) (Shimizu *et al*., 1998). Anti-apoptotic proteins may also protect cells from death by inhibiting the production of reactive oxygen species (Hockenbery *et al*., 1993; Kane *et al*., 1993), by preventing intracellular acidification (Gottlieb *et al*., 1996), by increasing mitochondrial Ca^{2+} capacity (Susin *et al*., 1996; Shimizu *et al*., 1998), and by providing overall stabilization of the membrane into which they are inserted (Vander Heiden *et al*., 1997; Zamzami *et al*., 1995). These pro-survival mechanisms are not well defined and may or may not involve the pore-forming capacity of anti-apoptotic proteins.

In the first model, Bcl-2-like proteins modulate OMM permeabilization without altering mitochondrial function, which means that $\Delta\Psi_m$ is maintained as well as ATP production. This is crucial because in the absence of dATP or ATP, the apoptosome cannot form, caspase-9 is not activated, and the cells tend to die by necrosis rather than by apoptosis (Chautan *et al*., 1999; Nicotera *et al*., 1999). The second model of OMM permeabilization involves mPTP, or megachannels, which form at contact sites between the outer and inner mitochondrial membranes (Zamzami *et al*., 1998; Zoratti and Szabo, 1995). Its core components are the voltage-dependent anion channel 1 (VDAC1), the adenine nucleotide translocator (ANT), the peripheral benzodiazepine receptor, the mitochondrial matrix cyclophilin as well as hexokinase and creatine kinase, which all create a large conductance pore permeable to solute with a molecular mass of ≤1.5 kDa (Bernardi *et al*., 1999; Crompton, 1999). mPTP opening results in mitochondrial depolarization and the subsequent dissipation of $\Delta\Psi_m$, uncoupling of oxidative phosphorylation, and swelling of the mitochondrial matrix (Bernardi *et al*., 1999). OMM rupture may eventually occur as a consequence of matrix expansion, releasing the intermembrane space contents (cytochrome c, DIABLO/Smac, Omni/HtrA2, AIF) into the cytosol in a nonspecific manner (Harris and Thompson, 2000; Zamzami and Kroemer, 2001). Interactions between some members of the Bcl-2 family and the components of mPTP have been proposed by several studies. Pro-apoptotic molecules like Bax could bind to ANT and promote mPTP opening, an effect prevented by the anti-apoptotic Bcl-2 (Marzo *et al*., 1998). The multidomains Bax and Bak could also interact with the VDAC1, enhancing its channel activity to allow passage of cytochrome c, while the BH4 domain of anti-apoptotic Bcl-2 and Bcl-xL rather stimulates closure of the channel (Shimizu *et al*., 1999; 2000; Shimizu and Tsujimoto, 2000). Recently, Sugiyama *et al*.(2002) have shown that the BH3-only Bim, but not Bid, may also interact with the VDAC1 and promote its opening, which results in loss of $\Delta\Psi_m$ and cytochrome c release. By interacting with mPTP, pro-apoptotic proteins thus appear to be capable of enhancing the basal permeability of mPTP, allowing molecules larger than 1.5 kDa to diffuse through.

BCL-2 FAMILY MEMBERS AND CELL-CYCLE CHECKPOINTS

In addition to their central role in controlling cell death, numerous studies have linked some Bcl-2-like family members with cell cycle progression (summarized in Fig.1). First, Bcl-2 itself was shown to slow entry from the quiescent G0 into the G1 phase of the cell cycle prior to DNA replication in multiple cell lineages and transgenic mice (Fig.1). In contrast, Bcl-$2^{-/-}$ knockout cells enter the S phase more quickly (Borner, 1996; Brady *et al*., 1996; Vairo *et al*., 1996; Mazel *et al*., 1996; Linette *et al*., 1996; O'Reilly *et al*., 1996; 1997a; 1997b; Huang *et al*., 1997; Knowlton *et al*., 1998; Ogilvy *et al*., 1999; Gillardon *et al*., 1999; Domen *et al*., 2000; Vail *et al*., 2002). This effect of Bcl-2 on cell proliferation is genetically distinct from its function on apoptosis (Borner, 1996; Brady *et al*., 1996; Vairo *et al*., 1996; Huang *et al*., 1997; Knowlton *et al*., 1998). Mutation of a tyrosine residue (Tyr28) within the BH4 domain has no impact on the ability of Bcl-2 to inhibit apoptosis and does not prevent its heterodimerization with death-inducing family members, including Bax, Bak, Bad, and Bik. However, when starved quiescent cells expressing the mutated protein are stimulated by serum, they re-enter the cell cycle faster than those expressing wild-type Bcl-2 protein (Huang *et al*., 1997).

Mcl-1, another Bcl-2 homologue known to function as an anti-apoptotic protein (Kozopas *et al*., 1993), inhibits cell-cycle progression through the S phase of

the cell cycle (Fig.1). The cell-cycle regulatory function of Mcl-1 is partially mediated through its interaction with proliferating cell nuclear antigen (PCNA), a cell cycle regulator that plays a critical role in DNA replication (Fujise *et al*., 2000). The binding motif for PCNA resides between the 221st to 228th amino acids of Mcl-1. Mutations introduced within this region do not alter the anti-apoptotic function of Mcl-1, but impede its binding to PCNA and significantly reduce its effect on cell cycle progression (Fujise *et al*., 2000). Thus, this effect of Mcl-1 on cell proliferation is genetically distinct from its function on apoptosis. More recently, others have revealed that a proteolytic fragment of Mcl-1 regulates cell growth via interaction with cdk1 (cdc2) (Jamil *et al*., 2005).

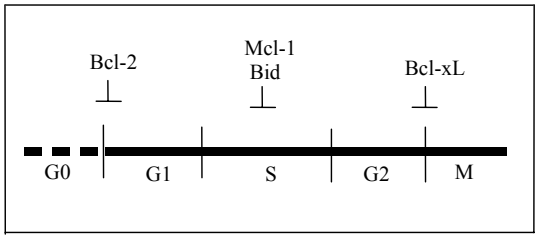

Fig.1 Schematic representation of the effects of Bcl-2, Mcl-1, Bid and Bcl-xL on cell cycle

Microtubule inhibitors widely used in cancer chemotherapy, including paclitaxel, taxotere, vinblastine and vincristine, induce mitotic arrest linked with Bcl-2, Bcl-xL and Mcl-1 phosphorylation (Haldar *et al*., 1995; 1996; Blagosklonny *et al*., 1997; Poruchynsky *et al*., 1998; Domina *et al*., 2000). However, studies have revealed that Bcl-2 and Bcl-xL phosphorylation is tightly coupled with normal mitotic events (Domina *et al*., 2000; Ling *et al*., 1998; Scatena *et al*., 1998; Fan *et al*., 2000a). Bcl-2 phosphorylation multisites (Ser70, Ser87, Thr69) are located within the unstructured loop domain of the protein, a region not essential for its anti-apoptotic function (Chang *et al*., 1997; Haldar *et al*., 1998; Fang *et al*., 1998; Srivastava *et al*., 1999; Yamamoto *et al*., 1999). Multiple kinases have been proposed to phosphorylate Bcl-2 (and presumely Bcl-xL), including an Ask1/Jun-N-terminal protein kinase 1 pathway, normally activated at G2/M (Fan *et al*., 2000a; 2000b; Yamamoto *et al*., 1999; Blagosklonny *et al*., 1996; Ruvolo *et al*., 1998; Srivastava *et al*., 1998; Maundrell *et al*., 1997; Kharbanda *et al*., 2000). In addition, Kharbanda *et al*.(2000) have reported that Bcl-xL is phosphorylated on Thr47, within the unstructured loop domain, and on Thr115, adjacent to the α3 helix of Bcl-xL, in response to ionizing radiation.

Recent works have also indicated a role for Bid in the intra-S phase checkpoint after replicative stress in response to DNA-damaging agents (Fig.1). This role of Bid is mediated through its phosphorylation at Ser78 and Ser61/64, by the DNA-damage kinase ATM (Zinkel *et al*., 2005; Kamer *et al*., 2005). More recently, we showed that in addition to its mitochondrial effect that delays apoptosis, Bcl-xL co-localizes and binds to cdk1 (cdc2) during the G2/M cell-cycle checkpoint, and its overexpression stabilizes a G2/M-arrest senescence program in surviving cells after DNA damage (Fig.1). Bcl-xL potently inhibits cdk1 (cdc2) kinase activities, which is reversible by a synthetic peptide between the 41st to 60th amino acids surrounding the Thr47 and Ser62 phosphorylation sites, and Asn52 deamidation site, within the flexible loop domain of Bcl-xL. A mutant deleted of this region does not alter the anti-apoptotic function of Bcl-xL, but impedes its effect on cdk1 (cdc2) activities and on the G2/M-arrest senescence program after DNA damage. The nuclear interaction of Bcl-xL and cdk1 (cdc2) suggests that Bcl-xL is coupled to the stabilization of a cell-cycle checkpoint induced by DNA damage, and this effect is genetically distinct from its function on apoptosis (Schmitt *et al*., 2007).

CONCLUSION

Recent progress in understanding the molecular mechanisms of DNA-damage response illustrates how the key components interplay into different processes to protect genomic integrity of cells. Already, strong efforts are being made by several laboratories to develop new compounds targeting cell-cycle progression, cell-cycle checkpoint and apoptosis regulatory proteins. Several natural products and synthetic chemicals occupied the BH3-binding site of anti-apoptotic Bcl-2 family members and some of these compounds promote apoptosis of tumor cells (summarized in Table 1) (reviewed in Reed, 2006). Knowing more about the molecular interdependence of the DNA-damage response network will certainly be helpful in designing rational therapeutic protocols

with these new compounds in combination with traditional chemotherapy. Insights into the dynamic nature of these processes and the spatio-temporal orchestration of their regulation will suggest novel potential therapeutic strategies to prevent and treat cancer in the near future.

Table 1 Natural compounds and synthetic chemicals targeting antiapoptotic Bcl-2 family members*

Compounds	Organization	Status
Genasense (antisense)	Genta, Inc.	Phase III
Gossypol	Ascenta (NCI-USA)	Phase I/II
Polyphenol E	Mayo Clinic (Mitsui Norin)	Phase I
GX-15-070	Gemin X (Canada)	Phase I
HA14-1 analogs	Raylight Chemokine Pharm. Inc.	Preclinical
ABT-737	Abbott Laboratories	Preclinical
Apogossypol	Burnham Institute/NCI-USA	Preclinical
BH3I-1/-2	Havard University	Preclinical
Antimycin A3	University of Washington	Preclinical
Compound 6	University of Michigan	Preclinical
Terphenyl derivative	Yale University	Preclinical

* From (Reed, 2006)

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