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Molecular Circuits of Apoptosis Regulation and Cell Division Control: The Survivin Paradigm

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Abstract The coupling of cell proliferation to cell death is thought to function as a pivotal crossroad, essential to preserve normal homeostasis and to eliminate dangerous cells before they divide. Survivin is a prototype molecule at this crossroad, intercalated in protection against mitochondrial cell death and orchestrating various aspects of cell division. Dramatically exploited in cancer and an unfavorable gene signature for disease outcome, the survivin pathway has now provided tangible opportunities for targeted, rational cancer therapy. J. Cell. Biochem. 92: 656–663, 2004.

Key words: survivin; apoptosis; cancer; IAP; stress response

OVERVIEW OF APOPTOTIC PATHWAYS

Apoptosis is generally defined as a genetic program of cellular suicide with unique morphologic characteristics that include chromatin condensation, membrane blebbing, and formation of so-called apoptotic bodies [Kerr et al., 1972]. This type of cell death is essential to sculpt the developing organism during embryonic and fetal growth [Meier et al., 2000], and is critical in the adult life to maintain the homeostasis of differentiated tissues [Hengartner, 2000]. Apoptosis is mediated by caspases, intracellular cysteine proteases that become activated in response to cell death stimuli, and cleave a variety of cellular substrates involved in DNA repair, cytoskeletal organization, nuclear integrity, and cell survival [Goyal, 2001].

Two main apoptotic pathways have been identified [Hengartner, 2000]. An "extrinsic" pathway critical for immune selection and inflammation [Krammer, 2000] is initiated by ligation of cell surface death receptors, including the TNFα receptor and CD95 (Fas) [Ashkenazi and Dixit, 1998]. This results in the formation of a supramolecular complex associated with the death receptors' cytosolic tail that promotes the activation of upstream caspase-8. Conversely, various intracellular or environmental stimuli converge on an "intrinsic" apoptotic pathway, which is characterized by increased mitochondrial leakiness and a global collapse of mitochondrial functions [Kroemer and Reed, 2000]. The enhanced mitochondrial permeability in turn results in the cytoplasmic release of noxious factors, including Ca^{2+}, reactive oxygen species, and proteins that facilitate caspase activation [Wang, 2001]. The apoptotic signal is then relayed downstream via the assembly of a cytoplasmic multimolecular complex, called apoptosome that promotes the activation of upstream caspase-9 by limited proteolysis or allosteric rearrangement [Kroemer and Reed, 2000; Wang, 2001]. The two apoptotic pathways exhibits extensive functional crosstalk, and caspase-8 cleavage of a Bcl-2 protein, Bid, amplifies cell death by activating mitochondrial apoptosis [Luo et al., 1998].

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Among the regulators of apoptosis, Bcl-2 proteins [Cory and Adams, 2002] act at the mitochondria to decrease (anti-apoptotic) or enhance (pro-apoptotic) permeability transition, typically by regulating cytochrome c release [Hengartner, 2000]. These molecules form homo- and hetero-dimers at the outer mitochondrial membrane, and the composition of the complex is thought to shift the balance between cell survival and cell death [Hengartner, 2000]. Among pro-apoptotic Bcl-2 family members, the "BH3-only" molecules Bax and Bak may be required to initiate most, if not all, mitochondrial-dependent apoptotic pathways [Wei et al., 2001].

The inhibitors of apoptosis (IAP) proteins comprise a second gene family of cell death regulators [Salvesen and Duckett, 2002]. IAPs' molecular signature is the presence of 1–3 copies of a ~70-amino acid zinc finger fold designated Baculovirus IAP repeat (BIR), which is conserved in related molecules from yeast to humans. Certain IAPs also contain a caspase-recruitment domain (CARD), a RING finger, a ubiquitin-conjugating domain, and a nucleotide binding P loop motif [Salvesen and Duckett, 2002]. IAPs have been implicated in two functions, protection from apoptosis and regulation of cell division. In mammalian cells, most, but not all, IAP proteins preserve cell viability by acting as endogenous caspase inhibitors [Salvesen and Duckett, 2002]. This pathway has been elucidated in detail with respect to kinetic of enzyme inhibition, structural coordinates of IAP-caspase complexes, and mapping of residues implicated in caspase binding [Shi, 2002]. Proteins released by mitochondria during permeability transition, including Smac/DIABLO, and potentially Omi/HtrA2, are thought to competitively bind to IAPs, and relieve their inhibitory interactions with caspases [Shi, 2002]. The anti-caspase activity of IAPs is evolutionary conserved, and *Drosophila* IAP-like proteins are essential regulators of cell survival in flies [Yoo et al., 2002]. Other cytoprotective functions of IAPs independently of caspase inhibition have been proposed including modulation of TGF-β signaling, SMAD-dependent transcription, and c-Jun amino-terminal kinase (JNK) activity [Birkey Reffey et al., 2001; Sanna et al., 2002]. Secondly, certain IAPs function as essential regulators of cell division. This is likely their ancestral role, as judged from the multiple meiotic/mitotic defects, chromosome missegregation, and polyploidy observed in gene deletion and knockdown experiments of IAP-like molecules in yeast [Uren et al., 1999; Li et al., 2000; Morishita et al., 2001] and *C. elegans* [Fraser et al., 1999; Speliotes et al., 2000].

SURVIVIN STRUCTURE–FUNCTION

Survivin is a structurally unique IAP protein [Salvesen and Duckett, 2002], organized as a stable dimer [Verdecia et al., 2000], and containing a single BIR and a −COOH terminus coiled-coil, but no other identifiable domain(s) [Ambrosini et al., 1997]. *Survivin* is a mitotic gene, whose expression at cell division is tightly transcriptionally-controlled [Kobayashi et al., 1999; Li and Altieri, 1999], and further regulated by rapid changes in protein stability mediated by polyubiquitination and proteasomal destruction in interphase [Zhao et al., 2000]. After cell cycle-dependent expression at mitosis, survivin localizes to various components of the mitotic apparatus [Li et al., 1998; Skoufias et al., 2000; Fortugno et al., 2002], including centrosomes, microtubules of the metaphase and anaphase spindle, and midbodies. A subcellular pool of survivin also localizes to kinetochores of metaphase chromosomes [Skoufias et al., 2000], potentially recruiting and regulating the function of molecules like Aurora B kinase involved in central spindle formation and cytokinesis [Wheatley et al., 2001]. The various mitotic pools of survivin are immunochemically distinct, suggesting that separate post-translational modifications may contribute to epitope accessibility and subcellular trafficking [Fortugno et al., 2002]. In this context, phosphorylation of survivin on Thr34 by p34cdc2-cyclin B1 [O'Connor et al., 2000a] or Thr117 by Aurora B [Wheatley et al., 2004] have been implicated in regulating protein stability and subcellular targeting to mitotic structures. In addition to the wild type survivin mRNA, two survivin isoforms are generated by insertion of an alternative exon 2 (survivin-2B, 165 amino acids) or removal of exon 3 (survivin-ΔEx-3, 137 amino acids) [Mahotka et al., 1999]. In survivin-ΔEx-3, the splicing event introduces a frame shift that generates a unique −COOH terminus [Mahotka et al., 2002] containing a bipartite nuclear localization signal [Rodriguez et al., 2002]. Intriguingly, a viral homolog of survivin-ΔEx3 has been described that localizes to

mitochondria and inhibits apoptosis via association with Bcl-2 and BIR-dependent suppression of caspase-3 activity [Wang et al., 2002].

DUAL FUNCTION OF SURVIVIN IN APOPTOSIS INHIBITION AND CONTROL OF MITOSIS

Three lines of experimental evidence support a role of survivin in suppressing cell death. First, over-expression of survivin inhibits apoptosis initiated via the extrinsic or intrinsic apoptotic pathways [Ambrosini et al., 1997; Kobayashi et al., 1999; Mahotka et al., 1999; Islam et al., 2000; Kasof and Gomes, 2000; Suzuki et al., 2000; Hoffman et al., 2001; Mirza et al., 2002; Zaffaroni et al., 2002]. Second, genetic manipulation of survivin in vivo caused phenotypes consistent with cytoprotection, either by enhancing cell viability in transgenic mice [Grossman et al., 2001a] or resulting in increased cell death after conditional allele inactivation [Okada et al., 2004]. Thirdly, molecular antagonists of survivin, including antisense, ribozymes, siRNA oligonucleotides or dominant-negative mutants caused caspase-dependent cell death, and enhancement of apoptotic stimuli [Li et al., 1999; Kasof and Gomes, 2000; Olie et al., 2000; Kanwar et al., 2001; Shankar et al., 2001; Xia et al., 2002; Yamamoto et al., 2002; Zhou et al., 2002; Choi et al., 2003; Pennati et al., 2003; Williams et al., 2003; Beltrami et al., 2004]. Recent evidence suggests that survivin cytoprotection may be more selective than that of other IAPs, and targeted at the upstream initiation of mitochondrial apoptosis. This is consistent with the formation of a complex between survivin and caspase-9 in vivo [O'Connor et al., 2000a], the ability of survivin to prevent caspase-9 activation within a functional apoptosome [Marusawa et al., 2003], and its modulation by binding to mitochondrially-released Smac/DIABLO [Song et al., 2003]. Moreover, cell death induced by survivin antagonists has the hallmarks of mitochondrial apoptosis with cytochrome c release [Mesri et al., 2001; Liu et al., 2004], apoptosome-dependent caspase-9 activation [O'Connor et al., 2000a], and loss of mitochondrial membrane potential [Beltrami et al., 2004].

In addition to cell death inhibition, survivin has also an essential role in mitosis. This first surfaced in targeting experiments using antisense or dominant-negative mutants, which resulted in a dual phenotype of spontaneous cell death (see above) and aberrant mitotic progression, with supernumerary centrosomes, multipolar mitotic spindles, failed cytokinesis, and multinucleation [Li et al., 1999]. Similar findings were obtained after inactivation of the *survivin* gene, in vivo following homozygous deletion [Uren et al., 2000], or tissue-specific conditional allele inactivation [Okada et al., 2004]. Recent data have suggested that survivin may contribute to multiple phases of cell division, including targeting of essential components of the central spindle midzone, Aurora B kinase and INCENP [Wheatley et al., 2001; Bolton et al., 2002; Honda et al., 2003], enhanced microtubule stability in metaphase spindle formation [Giodini et al., 2002; Tran et al., 2002], and regulation of the spindle assembly checkpoint [Li et al., 1998; Lens et al., 2003].

TRANSLATIONAL TARGETING OF THE SURVIVIN PATHWAY IN CANCER

One of the most significant features of survivin is its differential expression in cancer versus normal tissues [Ambrosini et al., 1997]. Reminiscent of "onco-fetal" antigens, survivin is strongly expressed in embryonic and fetal organs [Adida et al., 1998; Kobayashi et al., 1999], but undetectable or found at very low levels in most terminally differentiated normal tissues [Ambrosini et al., 1997], with the exception of thymocytes [Ambrosini et al., 1997], $CD34^+$ bone marrow-derived stem cells [Fukuda and Pelus, 2001], and intestinal basal crypt epithelial cells [Zhang et al., 2001]. By contrast, dramatic over-expression of survivin was demonstrated in most human tumors by in situ hybridization, RT-PCR, Western blotting, and immunohistochemistry [Altieri, 2003]. The selective over-expression of survivin in cancer appears to reflect a global deregulation of *survivin* gene transcription in transformed cells. This is consistent with the cancer-specific transcription of the survivin promoter [Bao et al., 2002], and the several oncogenic pathways that converge to up-regulate *survivin* gene expression in transformed cells. These include growth factor receptor signaling [Tran et al., 1999; O'Connor et al., 2000b], STAT activation [Aoki et al., 2003], PI3 kinase/Akt signaling [Dan et al., 2004] oncogene (Ras) expression [Sommer et al., 2003], and loss of tumor suppressor molecules, p53 [Hoffman et al.,

2001; Mirza et al., 2002], APC [Zhang et al., 2001; Kim et al., 2003], and PML [Xu et al., 2003].

From a translational standpoint, several retrospective studies have demonstrated that survivin expression in cancer is frequently associated with unfavorable disease outcome, abbreviated overall survival, increased rates of recurrences, resistance to therapy, and reduced apoptotic index, in vivo [Altieri, 2003]. Accordingly, profiling studies identified survivin as a "risk-associated" gene signature for unfavorable outcome in breast cancer [van 't Veer et al., 2002], large cell non-Hodgkin's lymphoma [Kuttler et al., 2002], and colorectal cancer [van de Wetering et al., 2002; Williams et al., 2003].

Because of its differential expression in cancer and critical roles in mitotic progression and cell viability, survivin is being intensely investigated as a new rational target for cancer treatment [Altieri, 2003]. Three approaches have recently emerged to interfere with the survivin pathway that showed promising results as potential anti-cancer strategies. First, survivin has been used for novel cancer vaccination protocols [Andersen and Thor, 2002]. Several studies have now demonstrated that T cells mount a vigorous cytolytic and antibody response to survivin peptides, in vitro and in vivo [Rohayem et al., 2000; Schmitz et al., 2000; Andersen et al., 2001; Yagihashi et al., 2001; Hirohashi et al., 2002; Schmidt et al., 2003]. Accordingly, HLA Class I-restricted cytolytic T cells against survivin peptides are found in cancer patients [Andersen et al., 2001; Schmidt et al., 2003], and exert strong antitumor activity when tested in preclinical models [Casati et al., 2003; Pisarev et al., 2003; Siegel et al., 2003]. Secondly, molecular antagonists of survivin, including antisense, ribozymes, siRNA, or dominant negative mutants have shown reproducible anti-tumor efficacy in vitro and various tumor models, in vivo inducing tumor cell apoptosis, suppression of cell proliferation, and collapse of tumor-associated angiogenesis [Grossman et al., 2001b; Kanwar et al., 2001; Yamamoto et al., 2002; Blanc-Brude et al., 2003; Williams et al., 2003; Ansell et al., 2004; Pennati et al., 2004]. Thirdly, molecular [Mesri et al., 2001] or pharmacologic [O'Connor et al., 2002c] antagonists of survivin phosphorylation on Thr34 have also shown promising results in suppression of tumor growth in mice, and enhancement of taxane-based chemotherapy.

A novel aspect of survivin cytoprotection in cancer has recently emerged with its link to the molecular chaperone Hsp90 [Fortugno et al., 2003]. Tumor cells are known to develop effective countermeasures to grow and disseminate in highly unfavorable microenvironments. This is mainly achieved via up-regulation of the cellular stress response, an evolutionary conserved process centered on expression/function of heat shock proteins (Hsps). Hsps are molecular chaperones that survey protein folding quality control, maturation, and subcellular trafficking of client proteins [Nollen and Morimoto, 2002], thus enabling cellular adaptation to environmental challenges [Helmbrecht et al., 2000]. Hsps, particularly Hsp70 and Hsp90 are also thought to have a function in protection from apoptosis, and are commonly up-regulated in various cancers [Neckers, 2002]. Binding to Hsp90 preserves survivin levels in cells and disruption of this interaction results in proteasomal degradation of survivin and a dual phenotype of spontaneous apoptosis and mitotic defects [Fortugno et al., 2003]. This is consistent with the notion that sudden changes in IAP levels brought about by ubiquitination and proteasomal destruction [Joaziero and Weissman, 2000] result in spontaneous apoptosis and enhancement of cell death stimuli [Yang et al., 2000; Li et al., 2002]. In this context, selective disruption of the survivin–Hsp90 interaction could be envisioned as an additional mean to destabilize the survivin pathway in cancer, promoting proteasomal degradation of survivin and enhanced caspase-9 activation [Fortugno et al., 2003].

CONCLUDING REMARKS

Despite its relatively recent discovery in 1997, survivin has attracted considerable interest from several viewpoints of biomedical sciences. Its dual implication in cell death regulation and mitotic progression, its deep wiring with fundamental checkpoints of genomic fidelity and its transcriptional regulation by a plethora of signaling pathways have positioned survivin at the crossroad of several fields of investigation in biology. With the elucidation of key molecular requirements of the survivin pathway, rational approaches to dismantle this signaling network in cancer cells have emerged, thus opening new translational opportunities for targeted cancer treatment in the near future.

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