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News and Views

Cytokinesis, apoptosis and survivin: Three for tango?

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Understanding how programmed cell death, or apoptosis, is regulated has proved an exciting but challenging task, ordering disparate gene families of adapter molecules, signaling partners and effector proteins. The stakes are obviously high because apoptosis has a fundamental role in sculpting the developing organism and in maintaining homeostasis of adult tissues. Recently, a group of molecules originally designated IAP for Inhibitor of Apoptosis, has entered the fray. Several eukaryotic IAPs are now recognized as suppressor of apoptosis. However, two recent papers[1,2] now demonstrate that certain IAP molecules homologous to the prototype survivin have a distinct role in cell division and cytoskeletal organization, and that interference with this process has dire consequences of dysregulation of mitosis and early embryonic lethality.

Originally discovered in the baculovirus for thwarting the host's suicidal response to infection, homologous IAP proteins have now been found in mammalian cells, worms, flies and yeast.[3] The identifying signature of these molecules is the presence of at least one ~70 amino acid zinc finger module designated baculovirus IAP repeat (BIR). It is this region that in several mammalian IAPs binds initiator and effector caspases, thus suppressing the enzyme's activity and/or interfering with its activation.[3] However, this is clearly not the only job that these molecules do, a safe hypothesis considering that IAPs have also been found in yeast that do not express caspases or undergo apoptosis. A diversified role of certain IAP proteins has been further reinforced by the identification of survivin, the smallest mammalian IAP protein carrying a single BIR.[4] Two features distinguish survivin from other IAPs. First, survivin is a mitotic protein, expressed in the G2/M phase of the cell cycle and localized to the mitotic apparatus,[5] and, secondly, it is the top fourth 'transcriptome', one of the 100 or so genes selectively expressed in cancer but not in normal tissues.[6] Now, experiments of RNA interference in *C. elegans* suggested that the survivin homolog in the nematode, *bir1* plays an essential role in chromosome segregation and cytokinesis.[1] Embryos or fertilized oocytes lacking *bir1* failed to properly align chromosomes for cell division, exhibited gross abnormalities of the spindle midzone and loss of proteins controlling the spindle checkpoint.[1] In particular, *bir1* targeting resulted in loss of co-localization of the *C. elegans* Aurora kinase, Air-2 to the spindle midzone, a molecule with a conserved role in microtubule nucleation and bipolar spindle formation.[1] Confirming earlier results of RNA interference,[7] loss of *bir1* did not influence apoptosis in *C. elegans*, and, conversely, suppression of the nematode cell death pathways did not rescue or modify the cell division defect induced by *bir1* targeting.[1]

So, how conserved is the pathways from nematode to mammals? Two lines of evidence suggest that in fact survivin-like molecules do play a general role in cell division. First, human survivin could partially rescue the mitotic defect induced by *bir1* deletion in the worm, thus allowing fertilized embryos to complete at least a few rounds of cell division.[1] Secondly, and perhaps more compellingly, mouse embryos in which the survivin locus had been disrupted by homologous recombination exhibited very early lethality with a phenotype very similar to that observed in the nematode.[2] Variable in onset between embryonic day 2.5 and 5.5, survivin knockout embryos exhibited gross nuclear abnormalities, with complete failure of cytokinesis and generation of giant multinucleated cells.[2] This was also associated with complete disorganization of tubulin function, with loss of mitotic spindles and intercellular midbodies and formation of large microtubule bundles further potentially hampering chromosome movements in anaphase. Overall, this defect was reminiscent of the early embryonic lethality observed after deletion of INCENP, a chromosomal passenger protein participating in chromosome segregation and microtubule dynamics,[8] and immunofluorescence labeling appeared consistent with a similar distribution of survivin.[2]

The demonstration of a direct role of survivin in cell division should not come as a complete surprise. The appearance of the knockout embryos and the defect in *C. elegans* are completely superimposable to the phenotype of survivin targeting obtained with antisense or a dominant negative mutant reported last year.[9] While the evidence that survivin molecules play a conserved role in cell division is strong and independently validated, much more challenging is the interpretation of what these molecules really do at mitosis. The defects induced by survivin targeting are complex, or, as they were previously defined, pleiotropic,[9] making it difficult to pinpoint the exact pathway modulated by these molecules. On the one hand, these defects are reminiscent of dysregulation of spindle checkpoint proteins affecting chromosome congression, a function not immediately obvious for BIR-containing proteins. A parallel with yeast is only partially informative.[10] Although a yeast IAP protein did bind the kinetochore Ndc10p protein, this interaction was mediated by the non-conserved –COOH terminus region, and removal of the BIRs did not affect kinetochore binding.[10] Similarly, the connection between survivin and Aurora rests presently in initial co-localization experiments: it is unclear if these molecules act in the same pathway, or whether the partial rescue of the *C. elegans* defect by survivin is due to re-targeting of Air-2 to the spindle midzone.[1] On the other hand, the defects induced by survivin targeting are typical

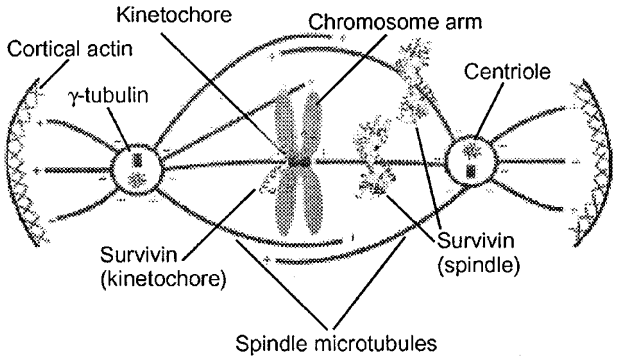

Figure 1 New roles and topography of survivin at cell division. The proposed localization of survivin in proximity with kitetochore proteins at metaphase is indicated. A previously reported association of survivin with mitotic spindle microtubules is also indicated. Both proposed survivin dimer interfaces are shown[11–13]

of profoundly disorganized microtubule function, like nucleation, assembly and dynamics. Survivin is clearly a microtubule-associated protein[5] and a component of the centrosome,[9] and potential requirements to mediate this interaction have clearly emerged from the crystal structure of the molecule[11–13] (Figure 1). However, preliminary experiments failed to suggest a role of survivin in microtubule dynamic instability, and its proposed role as a chromosome passenger protein must be further explored and some discrepancies with previous immunofluorescence data[5] unambiguously resolved.

If survivin molecules play a role in cell division, does this preclude their participation in apoptosis? Data from several laboratories argue against this thesis. In over-expression experiments, survivin has been invariably shown to protect cells from various apoptotic stimuli, albeit less well than other IAPs. Secondly, survivin expression can be induced independently of cell cycle progression, and this results in cytoprotection.[14] Thirdly, interference with survivin expression/function by antisense or dominant negative mutant invariably results in caspase activation and Z-VAD-inhibitable apoptosis, which can be temporally dissociated from a mitotic block and failure of cytokinesis.[15] And finally there is the cancer connection, where survivin is uniformly up regulated in all phases of the cell cycle, and has a critical requirement for tumor cell viability and suppression of apoptosis, *in vivo*.[16] So, can survivin dance two dances, and be involved in both the control of cell division and the regulation of apoptosis? After all, the BIR has evolved as a caspase-binding molecule,[3] and an interaction between survivin and caspase-9 *in vivo* has just been reported.[15] Then, one possibility is that survivin may have acquired a more evolutionary recent function in apoptosis control to integrate its original and primordial role in cell division. This hypothesis may have some evolutionary credibility since a *Drosophila* survivin molecule, deterin, acts as a genuine apoptosis inhibitor in the fly.[17] Clearly, this is just the beginning of an unfolding survivin saga. Although the elucidation of the crystal structure and the generation of knockout embryos are landmark advances, much work remains to be done to understand what these survivin molecules really do at a potential interface between apoptosis and cell division, and how this dance is cued on microtubules. One thing is certain, however. Molecular antagonists of survivin would make good drugs in cancer treatment, targeting what are clearly critical pathways of cell division and cell viability, selectively exploited in malignancies.

Acknowledgements

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