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REVIEW ARTICLE

Survivin: A target from brain cancer to neurodegenerative disease

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Abstract

Apoptosis is an important contributing factor during neuronal death in a variety of neurodegenerative disorders, including multiple sclerosis, Parkinson's disease and sciatic nerve injury. Whereas several clinical and preclinical studies have focused on the neuroprotective effects of caspase inhibitors, their clinical benefits are still unclear. Here, we discuss novel alternative strategies to protect neuronal cells from apoptotic death using members of the inhibitors of apoptosis (IAP) family. We specifically review the different roles of survivin, which is an important member of the IAP family that serves a dual role in the inhibition of apoptosis as well as a vital role in mitosis and cell division. Due to the various roles of survivin during cell division and apoptosis, targeting this protein illustrates a new therapeutic window for the treatment of neurodegenerative diseases.

Keywords: *survivin; neurodegenerative disease; apoptosis; neuroprotection; apoptosis inhibitor protein*

Introduction

Our understanding of neurodegenerative diseases has improved over the past few decades. Whereas these disorders are initiated due to a range of insults such as reactive oxygen species or misfolded proteins, all of these pathologies end with a common consequence, which is the degeneration and deterioration of neuronal cells (Kanwar, 2005; Kanwar *et al.*, 2009a). Despite efforts to understand and treat neurodegenerative diseases, their successful treatment has still not been achieved. A proper treatment should not only protect neural cells but should also increase their proliferation and differentiation so as to provide a promising future for an aging population and for families with a history of degenerative disorders, including multiple sclerosis, Parkinson's disease and stroke.

The brain's environment is the most protected part of our body and neurons are a unique cell type. Neurons play an important role in the analysis and transfer of information to the entire body, but the lack of neural self-proliferation and repair highlights the importance of their protection and proliferation. Protecting these cells from death and facilitating their proliferation involves mechanisms that still need to be identified. Experimental findings achieved over the past few years have suggested that inhibitors of apoptosis (IAP), which serve a natural role in balancing cell death, might be candidate proteins with a unique potential for drug discovery (Kanwar *et al.*, 2004a).

Here, an effort will be made to review the exceptional capabilities of survivin (a unique member of IAPs) in both cell cycle and cell death pathways and its unique characteristics related to neuronal cell survival and proliferation.

Cell cycle in neurons

A unique feature of neuronal cells is that they need to continuously hold their cell cycle in check (Herrup and Yang, 2007). Consequently, the intrinsic cascades of

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kinases, transcription factors and regulators of cell cycle seem to be inactivated. The entire CNS is composed of a few hundred ectodermal cells, called the neural plate, which rapidly develops into around 10^{11} neurons in the adult brain. In the developing CNS, neural stem cells form a polarized epithelium, known as the ventricular zone (VZ). Later, the second germinal region, known as the subventricular zone (SVZ), develops beyond the VZ. At the end of developing period, the VZ is depleted of all mitotic cells whereas the SVZ harbours precursor populations and gives rise to neurons, as shown in Figure 1 (Salomoni and Calegari, 2010).

Neuronal cells are born in the SVZ and cease to divide after migration from this neural layer. The absence of cell division is an important feature of neuronal cells. So, what happens if they fail to keep their cell cycle in arrest and start to divide? Several lines of evidence have shown that they eventually die. For example, it was shown that inactivation of the retinoblastoma (RB) protein followed by release of the transcription factor E2F1 increased the expression of cell cycle markers in adult neurons, while the M phase did not initiate and eventually caused the degeneration of neurons (Alubaidi *et al.*, 1992; Feddersen *et al.*, 1992). Additionally, there are reports from different laboratories regarding the expression of cell cycle markers including cyclins A, B, D and E, as well as CDK, PCNA and Ki67 in neurons of Alzheimer disease (AD) patients (McShea *et al.*, 1997; Nagy *et al.*, 1997; Arendt *et al.*, 1998; Busser *et al.*, 1998; Smith *et al.*, 1999; Yang *et al.*, 2001; Liu *et al.*, 2007). A similar situation has been reported in patients suffering from amyotrophic lateral sclerosis (ALS), Parkinson disease (PD), stroke and other neurodegenerative diseases (Jordan-Sciutto *et al.*, 2002; West *et al.*, 2005; Yang and Herrup, 2005; Burns *et al.*, 2007; Hoeglinger *et al.*, 2007).

The critical lesson from the above findings is that an appropriate treatment for neuroprotection and neuroproliferation not only needs to increase cell proliferation, but also needs to keep these neurons alive. According to previous findings, apoptosis (programmed cell death) has an active role in the development of neurodegenerative diseases and its blockage might lead to the protection of neuronal cells from deterioration (Kanwar *et al.*, 2004a; Bulat and Widmann, 2009).

Apoptosis

Programmed cell death or apoptosis is used by organisms to control cell numbers and to eliminate old and faulty cells. It is characterized by chromatin condensation, nuclear fragmentation (pyknosis) and cell shrinkage. Consequently, cells break up into small membrane-surrounded fragments called apoptotic bodies that are cleared by phagocytosis with no inflammatory response (Hengartner, 2000; Charriaut-Marlangue, 2004).

This self-controlling system can become invasive at any time, including when immune cells fail to recognize the correct target or in cases of disrupted gene expression. Apoptosis usually begins with a cell death signal that involves a series of external and internal pathways. The intrinsic signaling is associated with a series of events that include the following steps: (i) translocation of Bax, a Bcl_2 family member protein, from the cytosol to the mitochondria; (ii) deregulation of calcium channels, thereby increasing intracellular Ca^{2+} release and its overloading in the mitochondria (Wojda *et al.*, 2008; Marambaud *et al.*, 2009); (iii) depolarization of the mitochondrial membrane (Wang and Youle, 2009; Lanza and Nair, 2010); and finally (iv) release of cytochrome C (Charriaut-Marlangue, 2004), endonuclaese G (EndoG) (Li, LY *et al.*, 2001; Parrish *et al.*, 2001; Hahn *et al.*, 2004; Lordan *et al.*, 2009), apoptosis inducing factor (AIF) (Susin *et al.*, 2000; Loeffler *et al.*, 2001; Hagberg *et al.*,

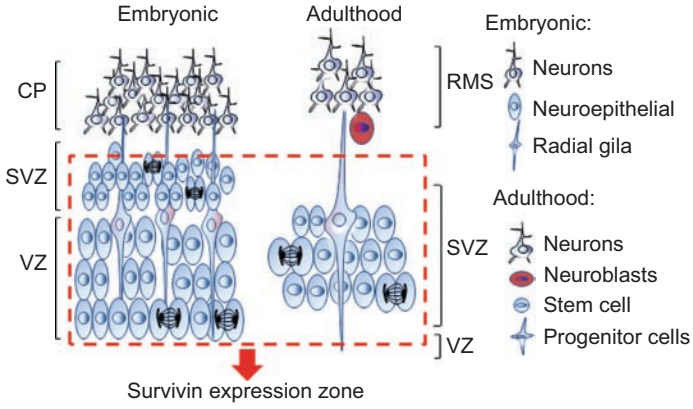

Figure 1. Survivin expression at two neurogenic niches: embryonic stage (left) and adulthood (right). The embryonic cortex is divided into cortical plate (CP), subventricular zone (SVZ), and ventricular zone (VZ). The adulthood lateral ventricle is divided into VZ, SVZ and rostal migratory stream (RMS) zones. The survivin expression zones are shown in the dashed box.

2009) and the second mitochondria-derived activator of caspase (Smac/DIABLO) (Srinivasula *et al.*, 2000; Martinez-Ruiz *et al.*, 2008).

Alternatively, the extrinsic pathway starts with the binding of the death ligand from tumor necrosis factor (TNF) to its receptor located at the cell surface. TRAIL and Fas ligand (FasL/CD95L) are members of the TNF family of death ligands (Ashkenazi, 2002). TRAIL binds to the death receptor 4 (DR4) and DR5 and transmits the apoptosis signal. FasL activates apoptosis by binding to the agonistic receptor Fas (CD95) and the soluble antagonist receptor dcR3 (Timmer *et al.*, 2002; LeBlanc and Ashkenazi, 2003). Trimerization of these receptors causes the formation of the death inducing signaling complex (DISC) (Ashkenazi, 2002).

Any of the mentioned events in both intrinsic and extrinsic pathways can initiate the next step of apoptosis. The major players of this step are the cysteine-dependent, aspartate–specific proteases known as caspases (Friedlander, 2003). They can be divided into the three following major groups according to their roles: Group I includes caspases 1, 4, 5 and 13, which have a major role during cytokine processing but a relatively unknown role during apoptosis due to their bulky hydrophobic amino acids (Wang and Lenardo, 2000; Charriaut-Marlangue, 2004). Group II includes caspases 2, 8, 9 and 10, which cleave the DExD motif site (found in most cleaved proteins during apoptosis), and is the primary executioner of apoptosis; Group III includes caspases 6, 7 and 3, which have a role during the cleavage of group II proteins by targeting their maturation site (Slee *et al.*, 1999; Wang and Lenardo, 2000). Antibody staining of newly exposed proteolysis-dependent epitopes of activated caspases or inhibition of degeneration by caspase inhibitors has demonstrated the importance of caspase activation in neurodegenerative diseases (Friedlander *et al.*, 1997; Ona *et al.*, 1999; Galvan *et al.*, 2006; Tanaka *et al.*, 2006).

Neuroprotection through caspase inhibition

Different peptides have been designed to directly inactivate caspases (Table 1). For example, use of broad spectrum caspase inhibitors such as z-VAD (pan caspase inhibitor) (Li, M *et al.*, 2000) or reversible inhibitors of caspase9 (z-LEHD-FMK) (Feng *et al.*, 2003) can reduce neuronal injury after hypoxic and cerebral ischemia injuries. In addition, Ac-YVAD-CMK (inhibitor of caspase1) protects against intracerebral hemorrhage injuries (Karaoglan *et al.*, 2008). Despite successful reports from different *in vivo* studies and short-term treatments, caspase inhibitors have been found to be ineffective for neuroprotection. The major limitation of caspase inhibitors is that the treated cells are not fully functional and may activate alternative pathways of cell death. For example, it has been shown that the pan-caspase inhibitor z-VAD-fmk modulates cell death through the activation of autophagy and necrosis (Kroemer, 2001; Brenner and Kroemer, 2000; Shimizu *et al.*, 2004). Similarly, z-VAD-fmk and a caspase3 inhibitor (Ac-DEVD-CHO) do not show any neuroprotective effects in a rat model of striatonigral degeneration (Mantoan *et al.*, 2005). One explanation for these failures could be due to the intracellular connections between different apoptotic and necrotic signaling

Table 1. Caspase inhibitors studied on brain cells.

Inhibitor	Caspase	Model	References
		Blood–brain barrier degradation	Wu *et al.* (2009),
Ac-YVAD-CMK [1]	Caspase1	Experimental spinal cord injury	Karaoglan *et al.* (2008),
Ac-WEHD-CHO [2]		Neurogenic pulmonary edema	Suzuki *et al.*, (2009),
		Transient cerebral ischemia	Hayashi *et al.*, (2001)
Z-VDVAD-FMK [3]	Caspase2	Chronic cerebral vasospasm	Aoki *et al.* (2002)
		Stroke	Havran *et al.* (2009),
3,4-dihydropyrimido		Glutamate toxicity	Ray *et al.* (2006),
(1,2-a)indol-10(2H)-	Caspase3	Traumatic brain injury	Knoblach *et al.* (2004),
(pyrimidoindolones)		Acute spinal cord injury	Citron *et al.* (2008),
z-DEVD-fmk		Transient cerebral ischemia	Hayashi *et al.* (2001),
zVAD-fmk [4]		Acute bacterial meningitis	Braun *et al.* (1999)
z-IETD-fmk [5]	Caspase8	Focal cerebral ischemia	Inoue *et al.* (2006),
		Limbic seizures	Li, TF *et al.* (2006)
z-LEHD-fmk[6]	Caspase9	Traumatic spinal cord injury	Colak *et al.* (2005),
		Paraoxon-mediated apoptosis	Wu *et al.* (2005)

[1]N-Ac-Tyr-Val-Ala-Asp-chloromethyl ketone
[2]Ac-Trp-Glu-His-Asp-CHO
[3] Z-V-D(OMe)-V-A-D(OMe)-FMK
[4]Carbobenzoxy-valyl-alanyl-aspartyl-[O-methyl]-fluoromethylketone
[5]Z-Ile-Glu(OMe)-Thr-Asp(OMe)-FMK
[6]Z-L-E(OMe)-H-D(OMe)-FMK

pathways (Proskuryakov *et al.*, 2003; Christofferson and Yuan, 2010).

Additionally, peptide based caspase inhibitors have low blood penetration and in most cases they have been applied intracereberoventriculary before or at the onset of neuronal damage (Rami *et al.*, 2008). Therefore, the relevance of obtained results from animal studies needs to be further clarified for the human situation. These results demonstrate that direct inhibition of caspase3 is not enough for the protection of neurons from neurodegeneration, and other apoptotic related elements need to be applied for successful protection (McLaughlin *et al.*, 2003).

Neuroprotection through natural inhibitors

Naturally, the brain is capable of adapting to stressful conditions and can respond to significant amounts of cellular destruction (up to 50%) (McLaughlin *et al.*, 2003) resulting from exposure to harmful stimulus. Usually, this process of preconditioning takes place through the production of natural inhibitors of apoptosis (Gidday, 2006).

Apoptosis is naturally controlled through a series of inhibitors known as the Bcl-2 and the inhibitor of apoptosis (IAP) family of proteins. They inhibit apoptosis through binding to activated caspases. The IAPs have at least one baculovirus IAP repeat (BIR) domain containing 70 amino acids. Eight members of this family have been recognized so far, including XIAP (X-linked inhibitor of apoptosis), cIAP1 (cellular IAP1), cIAP2 (cellular IAP2), survivin, livin/melanoma-IAP (ML-IAP), neuronal apoptosis inhibitory protein (NAIP) and Bruce (apollon) and ILP-2 (Salvesen and Duckett, 2002). These proteins are overexpressed (in particular cIAP1, cIAP2, XIAP and survivin) in almost all human tumor malignancies (Tamm *et al.*, 2000; Vucic and Fairbrother, 2007) while not much effort has been made to evaluate the expression of different members of IAPs during the neurodegenerative diseases. For example, while NIAP is downregulated in AD patients, XIAP is upregulated (Christie *et al.*, 2007). Also, lack of survivin expression has been found in degenerating neurons of *in vivo* models suffering from ALS (Tolosa *et al.*, 2008) and cerebral ischemia (Zhang, QG *et al.*, 2008).

Gene silencing and dominant negative forms of IAPs have been used for the treatment of different types of cancers and some of them are under phase II human clinical trials (Ryan *et al.*, 2009). Reportedly, transgenic mice overexpressing XIAP have more resistance to the occlusion of the middle cerebral artery (MCA) compared to controls (Trapp *et al.*, 2003). Additionally, in rat hippocampus that has been made resistant to transient forebrain ischemia, NAIP expression increases, and adenoviral delivery of NAIP has a protective effect against ischemic damage (Xu *et al.*, 1997). Furthermore, adenoviral delivery of NAIP, HIAP1 and HIAP2 into young rats has protective effects against sciatic axotomy (Perrelet *et al.*, 2000). The BH4 domain of Bcl-x_l attached to a TAT sequence (a membrane transport peptide) has neuroprotective effects. It can protect endothelial and neuronal cells against acute hypoxia/ischemia injury in rat brain during apoptosis (Donnini *et al.*, 2009).

During the early stages of brain development, expression of XIAP has been found to be essential. Survivin and XIAP have been found as dimers (Altieri, 2008) and it has been shown that the downregulation of survivin in neuroblastoma cells can lead to overexpression of its partners, XIAP, due to these network interactions (Russell *et al.*, 2008).

Among different members of the IAP family, survivin is a unique member with dual effects on cell cycle and apoptosis. Survivin, like XIAP, is essential for early brain development and disturbing its expression in the brain causes brain hypoplasty and embryos that only survive until birth (Jiang *et al.*, 2005). It is also shown that Birc5a (the zebrafish homolog of human survivin) depletion causes neurodevelopmental, hematopoietic, cardiogenic, vasculogenic and angiogenic defects (Delvaeye *et al.*, 2009). Interestingly, there is a high level of survivin expression in the ependyma and choroid plexus (CP). Additionally, analysis of neoplastic and paediatric ependymomas and CP tumors has revealed that the loss of nuclear survivin is associated with progressive cytologic anaplasia. These results indicate that survivin affects normal ependymal growth and neural stem cell differentiation (Altura *et al.*, 2003).

During immature excitotoxic brain damage, survivin was found in the nucleus of reactive astrocytes, in the damaged cortex and in the adjacent white matter area where it colocalized with cleaved caspase3 and protected astrocytes after injury (Villapol *et al.*, 2008).

Although the role of survivin as a potential target for cancer treatment has been well studied (Altieri, 2003; 2008; Kanwar *et al.*, 2001), as shown in Table 2, not much effort has been made to assess its potential for neuroprotection and neuroregeneration. Here, we review the different roles of survivin in the cell cycle and apoptosis and the potential impacts of neuronal cell therapy by means of survivin expression.

Survivin

Survivin is a member of the IAP family, and has a molecular mass of 16.5 kDa with a single IAP repeat domain and an extended carboxyl-terminal α-helical coiled-coil domain. However, it does not contain the RING-finger domain found in the other IAPs (Li, F and Ling, 2006).

Table 2. Natural apoptosis inhibitory members studied on brain cells.

Therapy	Mechanism	Effects	References
NIAP	Anti-apoptotic	Inhibit neuronal death induced by ischemia	Xu *et al.* (1997),
	Direct involvement in the intracellular response to glial cell-derived neurotrophic factor (GDNF)	Protect against sciatic nerve axotomy	Okada *et al.* (2005), Perrelet *et al.* (2002),
	Anti-apoptotic	Protect against NGF deprivation or TNF-α receptor stimulation	Gotz *et al.* (2000)
Bcl-X	Anti-apoptotic	Inhibit neuronal death induced by ischemia	Yin *et al.* (2006),
	Reduced cavity volumes and enhanced white matter sparing, Enhanced connectivity between the red nucleus and the spinal cord below the lesion and promotes graft survival and functional recovery	Protect against staurosporine-mediated apoptosis during transplantation in spinal cord injury	Lee *et al.* (2009),
	Increase the expression of cell cycle and neuronal markers	Enhance dopaminergic differentiation and survival	Teles *et al.* (2008),
	Decrease the calcium store in the endoplasmic reticulum	Protect against Bax-induced apoptosis in primary cultured astrocytes	Berman *et al.* (2009),
	Anti-apoptotic and increases plasticity protein GAP-43	Protect against hypoxia induced cell death	Gal *et al.* (2008),
	Drp1-dependent increases in synapse number, the number and size of synaptic vesicle clusters, and mitochondrial localization to vesicle clusters and synapses.	Synapse formation in cultured hippocampal neurons	Li, H *et al.* (2008), Liste *et al.* (2007),
	Increase the expression of cell cycle and neuronal markers	Modulates the differentiation of immortalized human neural stem cells	Dietz *et al.* (2007),
	Anti-apoptotic	Protect cerebellar granule neurons against the late phase glutamate-induced cell death	Hansen *et al.* (2007)
	Anti-apoptotic	Prevents spiral ganglion neuron death	
XIAP	Direct involvement in the intracellular response to glial cell-derived neurotrophic factor (GDNF)	Protect against sciatic nerve axotomy	Garrity-Moses *et al.*, (2006),
	Anti-apoptotic	Protect against glutamate neurotoxicity	Wootz *et al.* (2006),
	Inhibition of caspase 12 cleavage and reduce of calpain activity	Protect ALS spinal cord neurons	
	Larger b-wave amplitudes and decrease the number of TUNEL positive cells	Protect against retinal ischemia	Renwick *et al.* (2006),
	Anti-apoptotic	Protect against neonatal hypoxia-ischemia	Wang *et al.* (2004)
Bcl-2	Anti-apoptotic	Prevents spiral ganglion neuron death	Hansen *et al.* (2007),
	Anti-apoptotic	Prevents rat cortical neuronal injury caused by analogous ischemia/reperfusion	Hong *et al.* (2008),
	Anti-apoptotic	Prevents hypoxia induced neuronal death	Gal *et al.* (2008),
	Anti-apoptotic	Prevents amyloid-beta and prion toxicity in GT1-7 neural cells	Ferreiro *et al.* (2007),
	Increase of neural progenitor cells and decrease of apoptosis	Enhancement of neurogenesis and survival of new born neuron	Zhang, R et al. (2006)
Survivin	Anti-apoptotic	T-antigen-mediated protection neural progenitors	Gualco *et al.* (2009)
	Co-localization with heat shock protein 25/27 and anti-apoptotic	Protection of astrocytes after excitotoxicity to the immature brain	Villapol *et al.* (2008)

Human survivin is located on the telomeric position of chromosome 17 and spans 17.5 kb. It is transcribed from a TATA-less, GC-rich promoter to generate the wild-type transcript and four different splice variant mRNAs (Ambrosini *et al.*, 1997; Pennati *et al.*, 2007). Also, its activity is controlled through several post-translational modifications, including protein phosphorylation by $p34^{cdc2}$ and aurora B kinases, as well as ubiquitination (O'Connor *et al.*, 2000; Vong *et al.*, 2005). Survivin is known as a unique member of the IAP family due to its

bifunctional role in controlling both apoptosis and cell division (Li, F and Ling, 2006).

Survivin and neuronal cell division

During neurogenesis and before termination of neuronal production, each neuronal lineage undergoes 11 cell divisions. In the VZ of the developing brain most of the mitosis and cytokinesis occurs on the ventricular surface, whereas other cell cycle activities occur far from the ventricle. VZ is eventually depleted of dividing cells by the end of the developmental period. The next germinating zone, the SVZ, supports neurons during their final division and harbors stem cell precursor population in the adult (Miyata *et al.*, 2010; Farkas and Huttner, 2008; Shioi *et al.*, 2009). Survivin expression is required during early brain development (Jiang *et al.*, 2005), which demonstrates its vital role during mitosis due to its involvement in several intracellular networks that will be explained in the following sections (Figure 1).

Survivin and chromosomal passenger comple

Survivin has an intriguing function in the chromosomal passenger complex (CPC). CPC is a key regulator of mitosis and meiosis with three targeting and activating subunits, which include survivin, INCENP, and Borealin/Darsa B (Honda *et al.*, 2003; Gassmann *et al.*, 2004; Carmena, 2008). For complex formation, survivin dimerizes with Borealin as a monomer and with the aid of two small amino acids located on INCENP and Borealin, it proceeds to the central spindle during anaphase (Ruchaud *et al.*, 2007) (Figures 2A and 2B).

When survivin is present in the CPC, it guides the aurora B kinase to its substrate through its phosphorylation site at threonine 117 (Wheatley *et al.*, 2004). In addition, lack of an intact BIR (baculovirus inhibitor of apoptosis protein repeat), which is necessary for dimerization of survivin with INCENP, does not affect proper CPC localization to the central spindle (Skoufias *et al.*, 2000; Lens *et al.*, 2006), thereby suggesting that its regulatory domain is different from its dimerization domain. As we have shown in our previous study, a survivin BIR motif mutant is able to increase cell division in differentiated neuronal cells arrested in G0/G1 (Baratchi *et al.*, 2010), thereby suggesting that the survivin-dependent aurora B regulatory role is more important than its physical interaction in the CPC for correct chromosomal segregation and mitosis.

Survivin and microtubules

The highly dynamic structure of microtubules (MT), known as dynamic instability, is the key feature that facilitates cell division, migration or differentiation within neuronal cells (Demir *et al.*, 2009). In addition to survivin's contribution to CPC functioning, it also attaches to polymerized microtubules and contributes to microtubule stability (Altieri, 2006) (Figure 2C). Increases in survivin expression along with microtubule-associated protein-2 (MAP-2) have been reported following electric stimulation of a cereberal infraction site, which improves the recovery of motor function (Si, 2009).

Forced expression of survivin profoundly influences MT dynamics by reducing the pole-to-pole distance at metaphase while increasing MT instability against nocodazole induced depolymerization (Honore *et al.*, 2005). This shrinks centrosomal microtubule nucleation and suppresses both microtubule growth in midbodies during cytokinesis and microtubule dynamics in mitotic spindles (Rosa *et al.*, 2006).

Survivin is also necessary for the correct alignment of chromosomes on mitotic spindles and biorientation (capture of sister kinetochores by microtubules from opposite spindle poles) prior to anaphase (Makrantoni and Stark, 2009). This role is essential following a delay in spindle formation (Makrantoni and Stark, 2009), because spindle check points delay anaphase onset until all chromosomes have established biorientation (Vanoosthuyse and Hardwick, 2009).

Survivin intracellular balance

Nuclear-cytoplasmic transport of survivin, which occurs through the nuclear pore complex, is regulated by specific signals that bind to transport receptors and is active in all cell types, including neuronal cells (Weis, 2003). This nuclear-cytoplasmic transport is important since it can stipulate when survivin is needed in the nucleus for cell division or in the cytoplasm for apoptosis. This dynamic nature of survivin transport is controlled through a series of signals. Survivin export from the nucleus occurs through nuclear export signals (NESs) that function through dimerization with XPO1 (the human homolog of yeast Crm1), which is controlled by the Ran GTPase (Lippert *et al.*, 2007). NES-deficient survivin isoforms cannot localize to the cytoplasm, whereas NES-containing variants are cytoplasmic (Knauer *et al.*, 2007; Li, F, 2005).

Nuclear import usually occurs through short stretches of basic amino acids known as nuclear localization signals (NLSs) that cooperate with import receptors in the cytoplasm. Survivin import into the nucleus, however, occurs via passive diffusion rather than NLS activity due to its low molecular weight (Stauber *et al.*, 2007).

Furthermore, survivin and Ran form a complex that is independent of Crm1. This complex is essential for the delivery of the Ran effector molecule TPX2 to the microtubules and corrects mitotic spindle formation and chromosome segregation in tumor cells (Xia *et al.*, 2008).

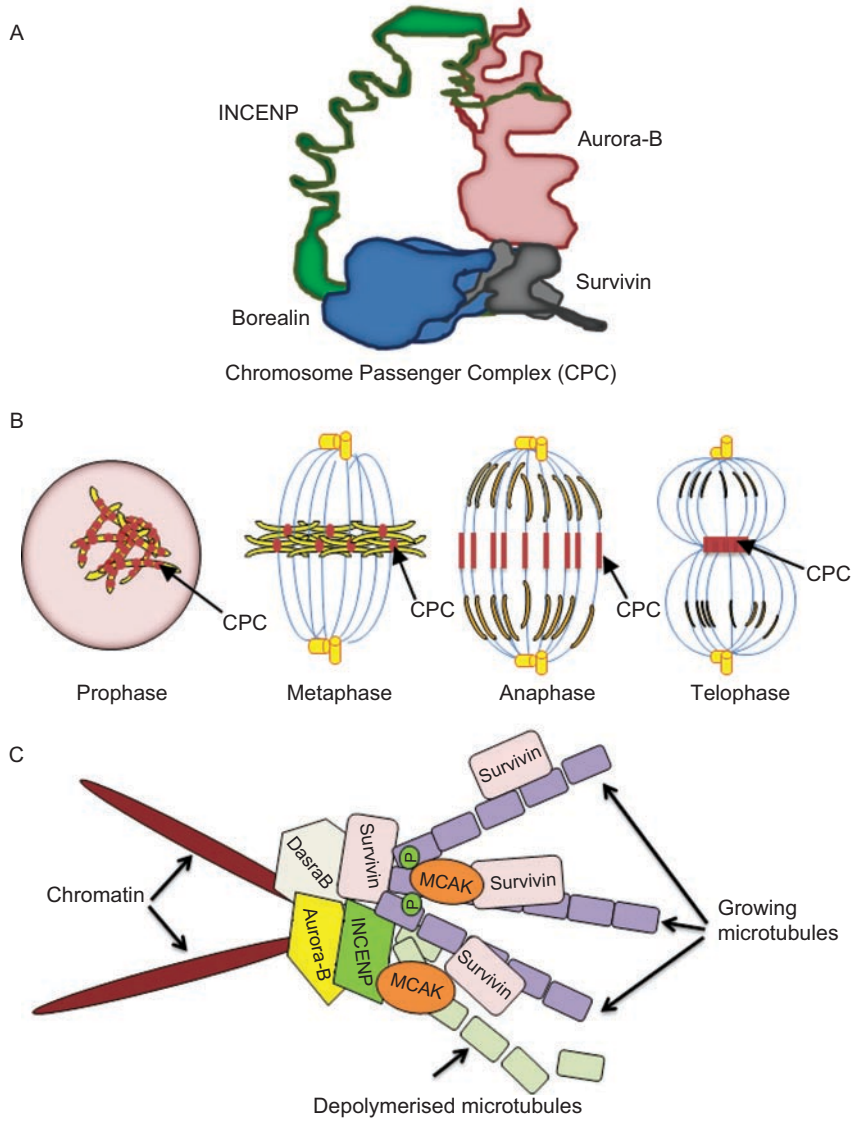

Figure 2. (A) Schematic location of survivin at chromosomal passenger complex (CPC). Survivin dimerizes with Borealin and interacts with two small amino acids located at the N-terminus of INCENP. The N-terminus of AuroraB binds to the IN box (amino acids 822–900) of human INCENP. (B) CPC localization during mitosis. In prophase the CPC locates at chromosome arms, in metaphase chromosomes align to the mitotic spindles and start to tense at kinetochores. In anaphase, CPC displaces to the spindle midzone and in telophase it is located at midbody. (C) Survivin location during spindle formation: survivin regulates the microtubule function through the CPC complex. Additionally, a separate pool of survivin exists attached to the polymerized microtubules, which contributes to the microtubule stability. AuroraB phosphorylation of MCAK eliminates its microtubule destabilization and helps spindle formation.

The subcellular localization of survivin in tumor cells suggests that cytoprotective survivin is located in the cytoplasm, whereas impaired survivin functions in the nucleus (Stauber *et al.*, 2007). In addition, several reports have indicated that nuclear survivin is associated with poor survival rates in cancer patients depending on the tumor type (Li, FZ *et al.*, 2005; Engels *et al.*, 2007). Future use of survivin for degenerative neurological diseases will likely show whether cytoprotective survivin can reduce damage to the CNS and whether nuclear survivin can increase the proliferation rate.

Survivin regulatory networks

Survivin expression at the subcellular level depends on different regulatory networks as explained below.

Transcription factor nuclear factor kappa B

The transcription factor nuclear factor kappa B (NF-kB) regulates different genes involved in inflammation, apoptosis and survival. It is activated during the development of brain injuries and aids in cell survival by increasing the expression of anti-apoptotic factors, including survivin

(Shishodia and Aggarwal, 2002; Burstein and Duckett, 2003; Nijboer *et al.*, 2008) (Figure 3A).

Abl is a non-receptor tyrosine kinase that is widely expressed in mammals and plays a major role in the development of different organs, including neurulation, neuronal dendritic maintenance and synaptic plasticity (Bradley and Koleske, 2009). Emerging evidence has suggested that tyrosine kinases are prominent players in several diseases, including neurological disorders (Bradley and Koleske, 2009). Inhibition of the oncogenic Bcr-Abl tyrosine kinase activates various signaling pathways, including the phosphoinositide 3-kinase/Akt pathway, whereas it downregulates nuclear factor-κB, leading to decreased expression of survivin, increased levels of p21 and p53, and inhibition of leukemia cell invasion (Monteghirfo *et al.*, 2008).

Ras family proteins

Ras family proteins, including the small GTPases H-, N-, and K-Ras, are key regulators of signal transduction pathways that control cell proliferation, survival, differentiation and apoptosis (Agell *et al.*, 2002). The best characterized Ras effector, the serine/threonine kinase Raf, leads to the activation of extracellular-regulated kinase (ERK), which plays a major role in cell proliferation and differentiation. Activation of the Ras/Raf/MEK pathway

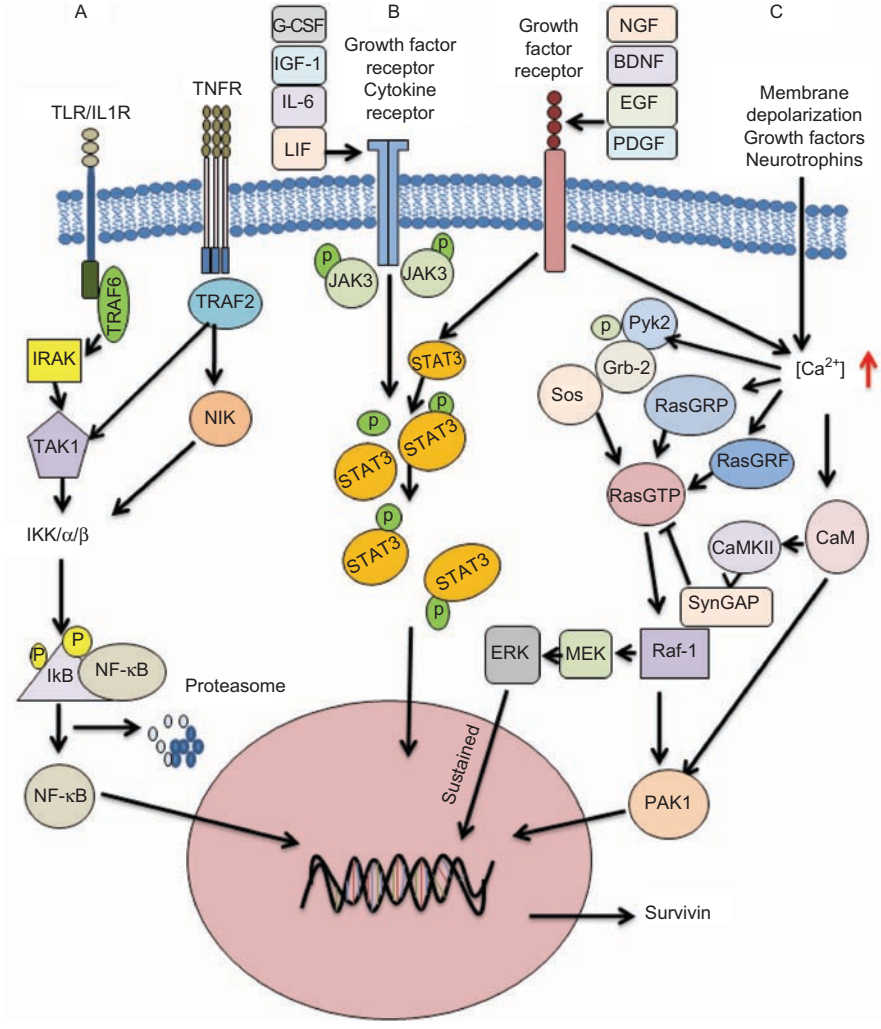

Figure 3. Survivin regulatory network. (A) Mechanism of cell survival and survivin expression through the NF-kB signalling pathway. TNFRs activate cellular responses through TNFR associated factors (TRAFs), including TRAF2 and TRAF6. Both of these TRAFs activate the kinases alpha and beta (IKK) directly or via NIK kinase. IKK then phosphorylates NF-kB inhibitor (I-kB). Phosphorylated I-kB is ubiquitinated and degraded via the 26S proteasome. This liberates NF-kB, allowing it to translocate from the cytoplasm to the nucleus to trigger the transcription of target genes, including survivin. (B) Mechanism of the STAT3 pathway. Cytokines, growth factors and the hormone estradiol (E2) lead to the phosphorylation and activation of STAT3, which is related to the neuroprotective roles of these factors following injury. STAT3 activation leads to the upregulation of several genes, including survivin. (C) Mechanism of Ras signalling and survivin expression in neurons. In response to an increase in cytosolic calcium, Ras and CaM mediate Raf activation and increase cell survival through survivin expression.

has also been shown to be involved in the overexpression of survivin, whereas dual inhibition of Raf/VEGFR2 significantly reduces survivin expression (Pumiglia and Decker, 1997; Roovers and Assoian, 2000; Agell *et al.*, 2002). PAK1, a MEK-independent Raf target, has been identified as a modulator of survivin expression. Survivin is a downstream regulator of PAK1 and controls osteoclast cell survival (Lang *et al.*, 2008). PAK1, a MEK-independent Raf target, has been identified as a modulator of survivin expression. Survivin is a downstream regulator of PAK1 and controls osteoclast cell survival (Bradley *et al.*, 2008) (Figure 3C).

Flt3 tyrosine kinase gene

The Flt3 tyrosine kinase gene (ITD-Flt3) can regulate survivin expression in primary hematopoietic progenitor cells. Survivin has an inhibitory effect on PI3-kinase induced apoptosis (Zhang, YH *et al.*, 2007). Furthermore, survivin may also affect cell viability by binding to the molecular chaperone heat shock protein 90 (HSP-90) (Fortugno *et al.*, 2003), and survivin expression might be dependent on HSP-90 (Jiang *et al.*, 2008; Okamoto *et al.*, 2008) and other cell cycle markers (O'Connor *et al.*, 2000).

Growth factors

Growth factors have also been shown to regulate the post transcriptional expression of survivin. One of these growth factors is IGF1, which plays an important role in the proliferation of a variety of cell types by protecting against mitochondrial damage and cellular apoptosis and increasing the expression of survivin (Hilmi *et al.*, 2008). Stimulation of IGF-1/mTOR in most cells results in increased survivin expression (Vaira *et al.*, 2007). The IGF-1 receptor (IGF-1R) is necessary for transformation of neuronal precursors by human polyomavirus JCV protein T-antigen and reactivation of survivin. In addition, JCV T-antigen-induced transformation is dependent on IGF-1R (Gualco *et al.*, 2009).

Natural tumor suppressor genes

Natural tumor suppressor genes often suppress the survivin promoter. These include p53, which is phosphorylated at Ser15. In addition, the affinity of p53 for the promoters proapoptotic genes, including survivin (Nieto-Rementeria *et al.*, 2009) is increased by Ser46 phosphorylation and methylation of survivin promoter can inhibits p53 binding (Nabilsi *et al.*, 2009).

Adenomatous polyposis coli (APC) gene mutations have been shown to activate Tcf4, a key transcription factor, and to modulate the expression of different proapoptotic genes, including survivin (Boman *et al.*, 2009). Fragile histidine triad (FHIT) is another tumor suppressor gene that has been found to function through tyrosine phosphorylation-dependent modulation of the Akt-survivin pathway (Pekarsky *et al.*, 2004; Semba *et al.*, 2006).

In addition, oncogenic factors have been shown to increase survivin expression. In this category, signal transducers and activators of transcription (STATs), a family of transcription factor proteins, mediate a wide variety of biological functions in both the central and the peripheral nervous system. In neurons and glia, STATs are expressed during development but are normally dormant in adult neurons. After injury, however, several STAT family members become activated, including STAT1, 3 and 5 (Dziennis and Alkayed, 2008). Among the different STATs, activated STAT3 is a key effector that boosts neuronal survival by inducing the expression of neuroprotective genes. Activation of STAT3 has been shown to induce survivin by binding to its promoter (Gritsko *et al.*, 2006; Dziennis and Alkayed, 2008). Inhibition of STAT3 decreases cell survival and increases apoptosis through caspase 3, 8 and 9 pathways by downregulating anti-apoptotic genes (Bcl-2, Bcl-xL and survivin) and cell cycle regulatory genes (cyclin D1) (Chen, CL *et al.*, 2008) (Figure 3B).

Survivin's role in inhibition of apoptosis

Apoptosis in the central nervous system (CNS) is one of the core features of acute and chronic neurological disease. In acute neurological diseases, apoptosis usually occurs in areas not severely affected by the injury, as in the spectrum of lesions in the ischemic brain, where collateral blood flow reduces the degree of hypoxia (Smale *et al.*, 1995; Troost *et al.*, 1995). In chronic diseases, on the other hand, apoptosis is the dominant form of cell death (Smale *et al.*, 1995; Troost *et al.*, 1995). The roles of survivin are mostly facilitated by interactions with other subcellular cofactors or adaptors, which partly explain the direct or indirect importance of survivin in different intracellular mechanisms.

One of the dominant roles of survivin is the inhibition of apoptosis, which is common to almost all cancer cells studied so far and occurs via an interaction with hepatitis B X-interacting protein (HBXIP). Survivin forms a complex with HBXIP and binds to procaspase 9 to inhibit apoptosis through the mitochondria/cytochrome c pathway, which depends on the formation of this complex (Marusawa *et al.*, 2003) (Figure 4).

Additionally, the dimerization of cytosolic survivin with its cofactor, XIAP, enhances its stability and inhibits apoptosis, although this complex formation can be disrupted by phosphorylation of survivin at Ser20 by cyclic AMP-dependent protein kinase A (PKA) (Dohi *et al.*, 2007).

In contrast, nuclear survivin forms a complex that is not involved in apoptosis but contributes to the control of cytokinesis. Cells overexpressing cIAP have been shown

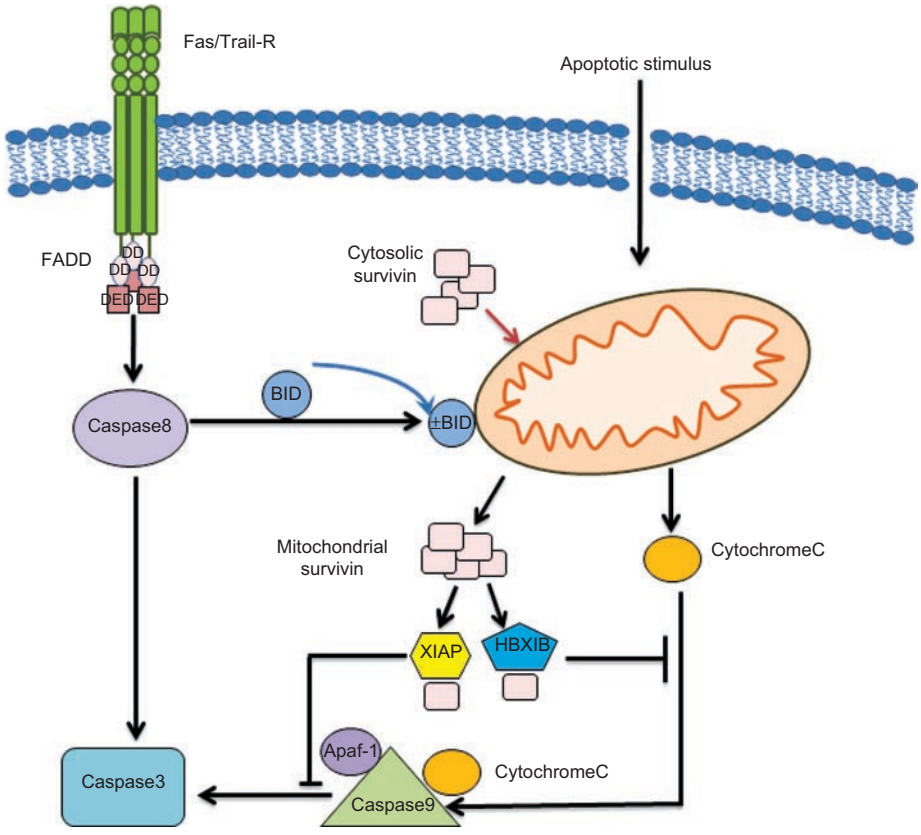

Figure 4. Survivin is an inhibitor of apoptosis. A pool of survivin is released into the cytoplasm from the mitochondria in response to cell death stimuli. This released survivin is a cofactor of HBXIB and XIAP and dimerises with either of them to inhibit caspase 9 activation and apoptosome formation.

to have defects in cytokinesis and display a mitotic checkpoint abnormality leading to the generation of polyploid cells. Survivin appears to have a role in antagonizing the function of cIAP in cytokinesis stability (Samuel *et al.*, 2005). Downregulation of survivin using small interfering RNA and dominant negative mutants has been shown to be associated with mitotic arrest and apoptosis, depending on the cell type (Kanwar *et al.*, 2001; 2004b; 2010).

Survivin and mitochondria

Mitochondria are the key links that connect the execution of neuronal cell death to cellular stress signals and are activated during neurodegenerative diseases (Jordan *et al.*, 2003). Additionally, any change in the mitochondrial transmembrane potential can increase free radical formation, deplete ATP and release different apoptotic factors, including cytochrome c (Jordan *et al.*, 2003). Furthermore, mitochondria contribute to the inhibition of apoptosis through the mitochondrial pool of survivin.

Activation of checkpoint kinase 2 (Chk2) followed by apoptosis signals causes the release of survivin from the mitochondrial pool to prevent DNA damage (Ghosh *et al.*, 2006). Survivin exists in the mitochondrial pool and is released into the cytosol in response to cell death signals, preventing caspase activation and inhibiting apoptosis (Dohi *et al.*, 2007). Although this pathway is independent of p53, p53 can reverse this effect by binding to the BIRC5 promoter, altering the chromatin structure, reducing survivin levels (Esteve *et al.*, 2005).

Most likely, the mitochondrial pool is involved in cancer formation, but it remains unclear how survivin is internalized into mitochondria. It is probable that this internalization occurs via the involvement of the chaperone proteins AIP and HSP90 (Fortugno *et al.*, 2003; Kang and Altieri, 2006; Cheung *et al.*, 2010). According to previous findings, most mitochondrial proteins are synthesized in the cytosol and transported into the mitochondria, probably via an N-terminal motif of precursor proteins and TOM20 and TOM70 receptor proteins located in the mitochondrial outer membrane. It is likely that survivin is also internalized through these receptors (Saitoh *et al.*, 2007).

As described earlier, one of the post transcriptional modifications that affect the anti-apoptotic role of survivin is the phosphorylation of survivin Ser20 by tyrosine kinase A (TKA) (Dohi *et al.*, 2007). This event occurs in the cytoplasm rather than in the mitochondria, likely due to the presence of Ser/Thr phosphatase PP2A and

the lack of TKA in mitochondria, leading to the dephosphorylation of imported survivin at Ser20 (Janssens *et al.*, 2005). Consequently, survivin is likely to be modified by binding to SMAC/DIABLO (Sun *et al.*, 2005), and then moves into the cytoplasm to activate XIAP and exert its anti-apoptotic effect.

In studying the neuroproliferative and protective effects of SurR9-84A, an IAP repeat mutant of survivin, we found a strong neuroprotective effect against the release of soluble inflammatory mediators from activated T-cells and hydrogen peroxide-mediated oxidative stress. These effects were due to the role of SurR9-84A in altering mitochondrial permeability, balancing calcium homeostasis and inhibiting apoptosis (Baratchi *et al.*, 2010).

Survivin variants and mutants

As mentioned above, wild-type human survivin consists of 142 amino acids and is encoded by four exons. Apart from wild-type survivin, 14 different variants have been reported thus far, but only four (Sur2α, Sur2B, SurΔEx3, Sur3B) have been studied comprehensively in terms of their anti- and pro-apoptotic effects and subcellular localization (Mahotka *et al.*, 2002; Badran *et al.*, 2004; Caldas *et al.*, 2005a; Song and Wu, 2005; Sampath, 2007).

The Sur3B variant has an intact BIR domain and zinc-coordinating amino acids and has been shown to have anti-apoptotic effects (Knauer *et al.*, 2007). Moreover, the Smac/Diablo interaction domain is intact in Sur3B, suggesting that this variant is able to interact with Smac/Diablo. There are different C-termini in Sur3B, and its BIR motif is interrupted by the deletion of exon 3. Although these differences from wild-type survivin might suggest the inability of this variant to have an anti-apoptotic effect, experimental results have shown otherwise (Caldas *et al.*, 2005b).

In the Sur2B variant, the Smac/Diablo interaction domain is interrupted by a 23-amino acid insertion. In addition, Sur2B and SurΔEx3 have reduced affinity for Borealin and therefore are not able to co-localize with the CPC complex (Noton *et al.*, 2006). Similar to wild-type survivin, Sur2B is present in both the nucleus and the cytoplasm, whereas SurΔEx3 is strictly nuclear and only exists in proliferating cells, not in G0/G1 arrested cells. Moreover, Sur2B is not anti-apoptotic, despite its cytoplasmic localization and NES domain, whereas SurΔEx3 is anti-apoptotic, despite its lack of an NES domain and its nuclear localization (Colnaghi *et al.*, 2006; Knauer *et al.*, 2006).

Although Sur2B and 3B are the only survivin variants that contain the domain required for dimerization, the ΔEx3 and 2α variants can also dimerize with wild type survivin (Caldas *et al.*, 2005b; Noton *et al.*, 2006). Wild-type survivin and Sur2B are expressed in the fetal brain, but not in the adult brain, whereas ΔEx3 is dominant in the fetal brain and is weakly expressed in the adult brain (Li, XN *et al.*, 2007).

Recently, three kinds of survivin variants have been found in human and mice, termed survivin-140, survivin-40 and survivin-121. The expression of survivin-140 and survivin-40 has been shown to increase following sciatic nerve injury, whereas no difference has been reported in the expression of survivin-121 (Amiri *et al.*, 2009). Apart from the different survivin variants that exist naturally, different mutant forms of survivin have been introduced, primarily for the purpose of structural analysis, and a few of them have been further evaluated as cancer therapies. The first survivin mutant, C84A, lies between highly conserved cysteine and histidine residues and is termed the survivin BIR mutant (Li, FZ *et al.*, 1998). The expression of C84A leads to apoptosis, maximal hydrolysis of amino acid sequence DEVD (a caspase 3 target) and aneuploidy in G2/M-synchronised cultures (Li, FZ *et al.*, 1998; 1999).

The Δ106 mutant lacks the C-terminus and does not localize to either kinetochores during metaphase or the spindle midzone or midbody during telophase. Both C84A and Δ106 have shown no interference with TD-60 (a known passenger protein) or cell cleavage (Skoufias *et al.*, 2000). A zinc binding site mutant, H80A, forms a smaller structure, probably a monomer (Muchmore *et al.*, 2000). In the D71A mutant, the dimeric organization of survivin and the negative charge around it are affected, leading to a proapoptotic effect. The E51A and L64A mutants have shown no effects on Hela cells, whereas the H80, E76 and G66 mutants have proapoptotic effects (Muchmore *et al.*, 2000).

The T34A mutant, which prevents phosphorylation at T34, suppresses TRAIL-induced apoptosis in variety of cancer cells (Table 3) and causes sensitivity to X-rays in glioblastoma cells (Chakravarti *et al.*, 2004; Eyers, 2009).

The D53A mutant has recently been reported to induce apoptosis in a p53-dependent manner. Similar to wild-type survivin, it is also able to localize to the cytoplasm during interphase and to the midbody during telophase, but it is not able to co-localize with aurora B kinase during metaphase. Furthermore, it has low stability and dimerizes with wild-type survivin, inhibiting its interaction with Smac/DIABLO (Song *et al.*, 2004). The DD70-71AA mutant can localize during metaphase to CPC complex but fails to accumulate at the kinetochore midbody during cytokinesis. Overexpression of the DD70-71AA has been shown to disturb cytokinesis, leading to multinucleation in Hela cells (Cao *et al.*, 2006).

Therapeutic strategies for survivin in brain cancer

Survivin is an ideal cancer target due to its tumor specificity and lack of expression in most normal differentiated

Table 3. Strategies being used to target survivin in cancer therapy.

Strategies	Compounds	Clinical stage	References
Inhibition of survivin function	Survivin-T34A	Ongoing preclinical study	Shen *et al.* (2009), Yan *et al.* (2006)
	Survivin-C84A		Zhu *et al.* (2006),
	Survivin-D53A		Cheung *et al.* (2006),
	Survivin-T34A,C84A		Zhang, R *et al.* (2008)
Repressor of survivin transcription factor	YM155	Phase I completed Phase II ongoing	Giaccone *et al.* (2009),
	EM-1421 (also called Terameprocol or M4N)	Phase I completed Phase II ongoing	Minematsu *et al.* (2009)
Targeting different pathways using small molecules	STAT3	Start of Phase I	Kunigal *et al.* (2009),
	CDK1 (flavopiridol)	Phase II ongoing	Dickson (2010), Lin *et al.* (2009)
	TCD (SDX-308)	Phase II ongoing	Lentzsch *et al.* (2007),
	HSP90 (17-AAG, BIIB021)	Phase I and II ongoing	Usmani *et al.* (2009)
Immunotherapy	DNA vaccine (survivin peptide)	Ongoing preclinical study	Fest *et al.* (2008),
	Survivin primed dendritic cells	Phase I and II ongoing	Kim *et al.* (2007)
Peptidomimetic	Shepherdin	Ongoing preclinical study	Gyurkocza *et al.* (2006)
Survivin translation repressor	Ribozymes RNA interference	Ongoing preclinical study	Fei *et al.* (2008),
	Anti-sense oligonucleotide		Tsuji *et al.* (2005)

cells with two exceptions so far, including normal testis and endometrium. In nearly all cancer cells, survivin is overexpressed, and its expression is higher in late-stage tumors, partly explaining the resistance of these tumors to treatments (Krepela *et al.*, 2009; Kanwar *et al.*, 2010). Due to the different subcellular networks that involve survivin, different strategies have been used to target survivin at both the gene and the protein levels.

The first strategy involves survivin antagonism and recruits molecules that directly target survivin. These molecules include LY2181308 (Dence *et al.*, 2005; Rodel *et al.*, 2006), YM155 (Kita *et al.*, 2009; Minematsu *et al.*, 2010), EM-1421 (Khanna *et al.*, 2006), in addition to dominant negative mutants such as transcriptional repressors, C84A and T34A, (Islam *et al.*, 2000; Chakravarti *et al.*, 2004; Kim *et al.*, 2004). The working mechanism of these small molecules is different from survivin antagonist. For example, LY2181308 acts as an antisense molecule while YM155 and EM-1421 act as transcription repressors, as follows. LY2181308 (a second-generation 2′-MOE ASO) is able to downregulate survivin expression leading to caspase3-dependent apoptosis in broad range of cancer cells (Chen, J *et al.*, 2000). Its antitumor activity is oligonucleotid sequence specific and associated with reduced survivin level in tumor cells (Gleave and Monia, 2005).

Alternatively, YM155 (a small imidazolium-based compound) can suppress the expression of survivin and induce apoptosis in p53-deficient human HRPC cells (Kaneko *et al.*, 2010), and is at phase II clinical trials (Satoh *et al.*, 2009; Giaccone *et al.*, 2009). It suppresses the expression of survivin but the exact molecular mechanism of YM155 is not clear (Kanwar *et al.*, 2010). Instead, EM-1421, also known as Terameprocol or M4N, is a semi-synthetic small molecule with antitumor activity via selective targeting of Sp1-regulated proteins such as survivin, and is at phase II of clinical trial (Lopez *et al.*, 2007).

The second strategy involves indirectly targeting survivin based on subcellular networks and immune responses. For example, the survivin-2B80-88 peptide has the ability to induce CD8-positive cytotoxic T-lymphocytes (CTLs). It is currently in phase I clinical trials and has been shown to be safe for patients with urothelial, breast and colorectal cancers (Tsuruma *et al.*, 2008; Honma *et al.*, 2009). Dendritic cells (DCs) expressing vectors with human survivin have also shown cytotoxic responses and prolonged tumor-free survival (Ciesielski *et al.*, 2006; 2010). In addition, the combination of TAT-survivin DCs with low-dose temozolomide (TMZ) improves the cell survival rate (Kim *et al.*, 2007).

A mimovirus vaccine is another example that has robustly protected mice against tumor challenges. This vaccine is a combination of the cell-penetrating peptide Tat49-57, a cytotoxic T lymphocyte (CTL) epitope, survivin 85-93 peptide and a plasmid encoding murine interleukin-15 (IL-15) (Yang *et al.*, 2008). Although the immunogenicity of survivin has been shown to be different using *in vitro* and *in vivo* studies, it has seldom been used in clinical trials.

Using the survivin promoter to drive cytotoxic genes is another indirect strategy that has been used for targeted expression of different pro-apoptotic proteins since it is more active in cancer cell lines than in normal cells (Bao *et al.*, 2002). This strategy has been used to target human telomerase reverse transcriptase (hTERT) (Wang *et al.*, 2007), to enhance radiation in malignant

glioma cells(Nandi *et al.*, 2008) and to induce transgene expression of mutant Bik in both *in vitro* and *in vivo* models to inhibit the growth of cancer cells (Chen, JS *et al.*, 2004). Many of these reported strategies are currently in the preclinical testing stage (Table 3) and require more comprehensive studies to assess their safety.

Conclusion and perspectives

In an effort to address issues involved with the treatment of neurodegenerative diseases, different aspects of survivin functioning over the past decades are reviewed here.

For the treatment of degenerative neurons, the two following strategies can be employed: a neuroprotection strategy and a neuroproliferative strategy. These findings suggest that Bcl2 and IAP inducers are able to inhibit apoptosis for the purpose of neuroprotection in preclinical animal models (Trapp *et al.*, 2003; Rami *et al.*, 2008). Among IAP family members, survivin appears to have the greatest therapeutic potential due to its unique role in mitosis and apoptosis, as summarized in this review.

Previous findings have identified the crucial role of survivin in early brain development probably due to its function in preserving cell viability and maintaining normal mitotic progression (Jiang *et al.*, 2005). Different subcellular pathways of the survivin network also suggest that survivin might be able to contribute in cell fate determination and differentiation (Altura *et al.*, 2003). These findings may suggest that survivin can be used for the proliferation and differentiation of progenitor cells for the future of neural transplantation and stem cell therapy of degenerative brain (Figure 5). Considering that apoptosis is an important cause of cell death during neurodegeneration, survivin as an important member of IAPs might be able to inhibit apoptosis and reduce the rate of damage in these cells (Figure 5). As survivin variants are not expressed in adult differentiated neurons, it is not likely that they interfere with survivin functionality, although this issue should be clarified in further studies.

The focus of this review was on targeting IAPs. In particular, we tried to highlight survivin as a candidate target for the treatment of neurodegenerative diseases. Inflammation is a well-recognized aspect of the pathology of neurodegenerative diseases, and different aspects of anti-inflammatory therapies have been reviewed elsewhere. Still, we must stress the importance of future studies on the synergistic effects of anti-inflammatory and antioxidant therapies or targeting adhesion molecules and co-stimulatory therapies, in addition to targeting survivin. Since survivin is expressed in stem cells and some progenitor cells, survivin therapy can increase the rate of proliferation. To minimize the side effects associated with exploitation of wild-type surviving, such as tumor formation, variant or mutant forms of survivin can be applied.

Further experiments are needed to evaluate the effectiveness of survivin therapy in animal models. Penetrating survivin across the blood brain barrier (BBB)

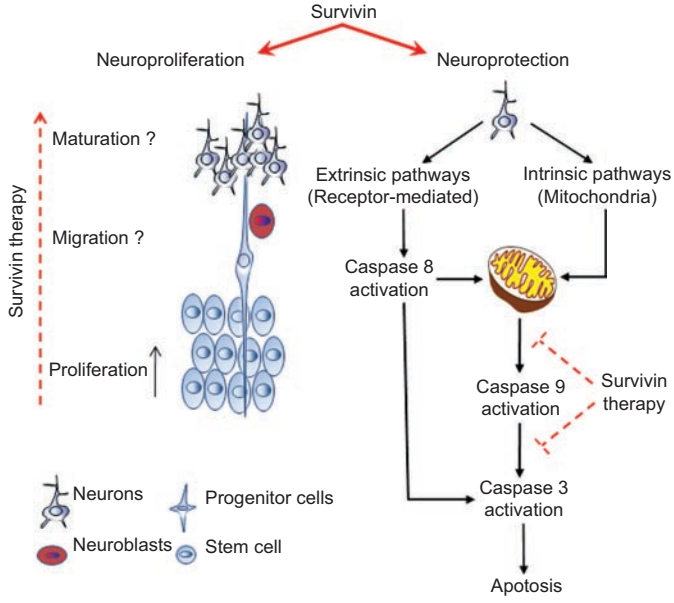

Figure 5. Possible strategies for the application of survivin in treatment of neurodegenerative diseases. Left: survivin can be applied to increase the proliferation of stem/progenitor cells; however its ability for initiating the neuronal migration or maturation needs to be clarified. Right: during neurodegeneration, apoptosis is activated via the extrinsic (death receptor) or intrinsic (mitochondrial) pathways. Survivin, as the IAPs member, can be applied to inhibit apoptosis by targeting caspase9 and 3 and therefore reducing the rate of neuronal damage.

is a challenge that could be resolved using nanotechnology approaches if safety issues are addressed (Baratchi *et al.*, 2009; Kanwar *et al.*, 2009b).

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