

Nuclear Survivin: Cellular Consequences and Therapeutic Implications

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1. Introduction

Survivin is a cancer associated protein that is present in all embryonic cells, but whose expression is normally limited to actively proliferating cells in adults. During mitosis it is part of a conserved complex of chromosomal passenger proteins (CPPs), which is essential for chromosome biorientation and cell division (Ruchaud et al., 2007). Defects in CPP function cause errors in mitosis and cytokinesis and can lead to genomic instability, or “aneuploidy”, a status indicative of tumorigenesis. First discovered by Altieri and co-workers (Ambrosini et al., 1998), survivin is the fourth most upregulated mRNA in the cancer transcriptome (Velculescu et al., 1999), and in many tumours its expression is detected throughout the cell cycle. Importantly increased survivin abundance correlates with tumour resistance to conventional radiation and chemotherapies, a correlation recapitulated in cultured cells in the laboratory (Chakravarti et al., 2004; Colnaghi et al., 2006). While involvement in mitosis alone is a valid reason for considering a protein as a biomarker, or a target for cancer therapy, the oncotherapeutic potential of survivin is compounded by the fact that it is also an inhibitor of cell death (for review see Altieri, 2008). The principle aim of this article is to highlight the manifestations of survivin expression in the nucleus and to discuss how these might be exploited for oncotherapeutic gain.

2. Subcellular localisation of survivin as a prognostic marker in cancer

Numerous clinical studies have reported differential localisation of survivin in the cytoplasm, the nucleus, or both in tumours and have correlated this with disease severity and patient survival, with the aim to determine the prognostic value of its localisation retrospectively. However, despite the plethora of data collected, the prognostic significance of the subcellular distribution of survivin in cancer remains unclear. In 2005 a review of the subject returned a hung jury, revealing more opposing conclusions and contradictions than commonalities (Li et al., 2005); see also (Xie et al., 2006). As most of these clinical-based studies used histopathological samples, the lack of uniformity in sample collection and preservation between labs, together with differences in antibody protocols and the subjective nature of the analysis are likely to have contributed to the variation within these data (Li et al., 2005). Differences in data acquisition and interpretation aside, survivin localisation does vary between tumour types, and if one considers more detailed factors within specific types of cancer, such as its grade, stage of differentiation, and whether it is

benign or malignant, this approach could yield fruitful predictions. Indeed, Gallagher, Duffy and co-workers have recently validated this approach in tumour microarrays of breast cancers, in which they have recorded not just the cytoplasmic and nuclear placement of survivin in tumours, but the ratio between their distributions. Their automated analysis clearly removes the subjectivity of the interpreter, and also permits its application to high through-put screening (Brennan et al., 2008; Rexhepaj et al., 2010). In summary, while survivin's subcellular localisation may have prognostic value across a wide spectrum of tumours, correlating its distribution, or the ratio of its distribution with disease outcome within specific tumour types may be more effective.

3. Active export keeps survivin out of the nucleus

In an attempt to determine the biological significance of cytoplasmic versus nuclear localisation of survivin, and prompted by the ongoing debate regarding its prognostic potential in cancer, we (Colnaghi et al., 2006), and others (Knauer et al., 2007) began to investigate and manipulate survivin distribution in controlled conditions in the lab. These data have led to the widely accepted view that survivin is predominantly cytoplasmic in interphase cells (Figure 1A), gaining access to the nucleus in G₂, in readiness for mitosis. While this is consistent with the cell cycle regulation of survivin transcription, it is in fact an oversimplification. One notable exception is exemplified by Temme and coworkers (2005), who reported that in exponentially growing normal human lung fibroblasts endogenous survivin is predominantly nuclear throughout the cell cycle. Interestingly they found that survivin localisation was age dependent, with cells from an early passage exhibiting strong nuclear accumulation, while cells of late passage (>16) displaying mostly cytoplasmic survivin. In full corroboration with other reports, survivin expression was absent from confluent G₀ monolayers of these cells (Temme et al., 2005). Moreover, other groups have indicated that survivin can enter the nucleus as early as S-phase (Beardmore et al., 2004; Suzuki et al., 2000). These observations highlight the fact that multiple parameters including cell type, senescence and growth conditions can impact on survivin localisation, and suggest that many pathways contribute to its whereabouts both spatially and temporally. Indeed many subcellular pools of survivin exist, including an important fraction within the mitochondria (Dohi et al., 2007; Fortugno et al., 2002), and several groups have hypothesised that these separate pools correspond to the distinct functions of this "nodal" protein, see review by Altieri, 2008.

The first evidence that survivin actively shuttles between cytoplasmic and nuclear compartments, came from the work of Rodriguez and coworkers, who used the fungal toxin leptomycin B (LMB) to demonstrate that its cytoplasmic localisation was maintained by CRM1/exportin- mediated transport, stimulated by Ran-GTP (Rodriguez et al., 2002). Using site-directed mutagenesis we (Colnaghi et al., 2006), and others (Knauer et al., 2007), identified a leucine-rich region in the central "linker" region of survivin between the BIR (baculovirus inhibitor of apoptosis repeat) domain, and its alpha-helical C-terminus as a nuclear export sequence (NES). Although clearly positioned within the central linker domain, estimations of the precise residues involved, 89-98 and 96-106, did not fully agree. Within a classic NES hydrophobic leucines are key as they are responsible for interaction with the CRM1 (exportin) via Ran-GTP, and despite the difference between our proposed sequences, there was consensus that both encompassed L96 and L98, with the sequence

proposed by (Knauer et al., 2007), more efficient at binding CRM1. Given the variance in the above studies and the proximity of the proposed NES to its homodimerisation interface (Verdecia et al., 2000), Engelsma et al., (2007) investigated this region in more detail. They proposed that residues 84-109, shown in red on the crystal structures in Figure 2, constitute a more complete sequence for the central NES. Furthermore, by mutating F101 and L102 to inhibit homodimerisation, they found that survivin was more efficiently removed from the nucleus than the wild type form, suggesting that monomeric survivin is more efficiently exported than homodimeric survivin. These authors further reported a second, unconventional NES present in the C-terminus of survivin, depicted in orange in Figure 2, and spanning the alpha-helix from residue 119 to its end (Engelsma et al., 2007; Rodriguez et al., 2002). Presumably this second NES would be operative in both monomers and dimers, and would act to further ensure survivin removal from the nucleus.

Trafficking of survivin between the nucleus and cytoplasm is also susceptible to regulation by post-translational modifications, including acetylation and phosphorylation. Survivin acetylation, which occurs at K129, and is facilitated by the acetyl transferase CREB-binding protein (CBP), has been implicated in aiding survivin transit out of the nucleus (Wang et al., 2010), presumably by affecting the activity of the C-terminal NES (Engelsma et al., 2007). Glucocorticoid synthase kinase 3 β (GSK3 β) facilitates translocation of survivin into the nucleus, but whether phosphorylation of survivin by GSK3 β is involved is not yet known (Li et al., 2008). Work from my lab has recently provided two lines of evidence that suggest that casein kinase 2 (CK2) phosphorylation helps to maintain survivin within the cytoplasm, as treatment with the CK2 specific inhibitor, TBB (4,5,6,7-tetrabromobenzotriazole), or mutation of threonine 48 (T48), the unique site targeted by CK2 in survivin, causes its accumulation in the nucleus (Barrett et al., 2011). This latter observation is curious because T48 lies in the BIR domain of survivin, which is from distinct from either NES, and would not affect binding to CRM1. Perhaps CK2 affects survivin import or its stability?

4. Getting into the nucleus

The molecular weight cut off for passive import across the nuclear membrane is approximately 45kD, thus at 16.5 kD survivin is sufficiently small to access the nucleus by passive diffusion even as a homodimer, or as a monomer tagged with a large fluorescent moiety such as green fluorescent protein, GFP (27kD). Whether an active component contributes to its import is unclear, but is supported by the observation that transit from the cytoplasm to the nucleus is abrogated when cells are chilled (Rodriguez et al., 2002), and would have the potential for its regulation, as suggested above for CK2, which could be exploited under challenging or stressful conditions. As survivin itself has no recognisable nuclear localisation signal (NLS) of its own, to facilitate nuclear entry survivin would presumably require a chaperone. While its mitotic partners, borealin, inner centromeric protein (INCENP) and aurora-B all have one or more NLS, co-expression analysis demonstrated that none of them can coerce survivin into the nucleus, instead, when co-expressed with borealin, borealin no longer localises to the nucleoli but is forced to relocate to the cytoplasm (Rodriguez et al., 2006). This is somewhat surprising given that borealin interacts with survivin at its homodimerisation interface and could potentially mask part of the central NES (Figure 2B), nevertheless, it points to the subtleties lying within the structure

of this tiny protein. As mentioned above redistribution of survivin into the nucleus is promoted by activation of GSK3B, and although it is not yet known whether survivin is a substrate of this kinase, GSK3B can bind survivin directly and has a bipartite NLS (Li et al., 2008).

5. Isoforms

In addition to “wild type” survivin, alias survivin-alpha/BIRC5, several splice variants exist. The two most extensively studied are alternatively spliced at the exon 2-intron border, which generates the variants, survivin 2B, with an additional 23 aa after exon 2, and delta exon 3 (DeX3) which incurs a frame shift that results in a completely distinct C-terminal sequence (Mahotka et al., 2002; Mahotka et al., 1999). We, and others, have shown that consistent with the central positioning of the NES, 2B retains this sequence and is predominantly cytoplasmic when ectopically expressed in cultured cells, while DeX3 is nuclear, not only because it lacks the two NES sequences, but because it has its own, functional NLS in its C-terminus (Mahotka et al., 2002; Noton et al., 2006; Rodriguez et al., 2002). As for the nuclear-cytoplasmic debate, the prognostic importance of the expression of these forms is also a matter of controversy, and there are many reports correlating the expression of transcripts of these variants and localisation of their gene products with disease severity, most recently (Antonacopoulou et al., 2011) and (Takeno et al., 2010).

6. Consequence of nuclear residence

To determine the consequences of expressing survivin in the nucleus we fused survivin cDNA to an NLS and transfected it into cultured human cells (Colnaghi et al., 2006; Connell et al., 2008a). Upon expression we noted the abundance of NLS-survivin was significantly reduced compared with wild type survivin, present in the cytoplasm. Moreover the levels of survivin-NLS in the nuclear fraction could be restored by treatment with the proteasome inhibitor, MG132, or siRNA mediated depletion of the APC/C activator *cdh1*. From our data we concluded that coercing survivin into the nucleus facilitated its removal from the cell in a 26S-proteasome/*cdh1* dependent manner (Connell et al., 2008a). Hence, in addition to import-export dynamics, stability is another key determinant of intranuclear localisation of survivin.

But why is it so important to keep survivin out of the nucleus? From our data on the accelerated clearance of NLS-survivin, and the presence of two NES sequences, it is clear that the cell has put in place multiple measures to eliminate survivin from the nucleus, so what are the consequences of its presence should it become resident there? In an early study by Suzuki and co-workers (2000) it was noted that upon release from serum starvation ectopically expressed survivin accumulated in the nucleus of human hepatoma cells. Interestingly they found that translocation of survivin to the nucleus coincided with an S-phase shift. At the molecular level they explained this precocious entry into S-phase as a downstream consequence of a direct interaction between survivin and *cdk4*. In essence, upon binding to *cdk4* survivin competitively inhibits the interaction between *cdk4* and *p16^{INKa}*, *cdk4*'s natural inhibitor, allowing *cdk4* to activate *cdk2/cyclin E*, which in turn hyperphosphorylates *pRB* derepressing transcription, and promotes passage through the G1 restriction point (Suzuki et al., 2000). Survivin-induced S-phase promotion has also been

noted in breast cancer cells, T-lymphocytes, and haemopoietic cells, reviewed in (Fukuda and Pelus, 2006). Thus one manifestation of nuclear residence is accelerated entry into the cell cycle.

A second consequence of nuclear residence of survivin is the loss of its cytoprotective activity. Converging data from analysis of NES mutants (Colnaghi et al., 2006), NLS fusions (Connell et al., 2008a), LMB treatment (Knauer et al., 2007), GSK3 β -activated cells (Li et al., 2008), and the response of cells in which nuclear survivin naturally occurs (Temme et al., 2007), have clearly demonstrated that nuclear survivin can no longer inhibit cell death, invoked by either the intrinsic or extrinsic apoptotic pathways. An apparent paradox here is that while cytoplasmic localisation of survivin is a requirement for it to protect cells from irradiation (IR), irradiation itself induces translocation of survivin to the nucleus (Chakravarti et al., 2004). In our hands, IR induces nuclear foci of survivin, which form as early as 60 minutes post-IR and can persist for many hours (Figure 1B), although a more dynamic response has been noted by others (Capalbo et al., 2010). This paradox, however, may be explained in part by data from Chan et al., (2010) who recently reported that during early stages of cell death, the CRM1/exportin pathway collapses. Although in their case retention of survivin in the nucleus as a result of compromised export, resulted in its rapid Ub-proteasome dependent rapid clearance (Chan et al., 2010), it is formally possible that failed export contributes to an initial sequestration of survivin in the nucleus, which may be followed by an altered rate of turnover, and eventually focus formation. Another plausible explanation for these data may be that the cells are arresting in G2 in response to DNA damage and that this is a time when survivin normally enters the nucleus in preparation for mitosis. Whatever the means by which these foci form have been shown to colocalise with the DNA damage marker, gamma-H2AX, and the DNA repair proteins, DNA-PK and Ku70 (Capalbo et al., 2010). Moreover, survivin translocation may be effected by the downstream chk1 and chk2 effector kinases, which respond to the PIK-family of kinases, ATR and ATM respectively, both pivotal upstream kinases in the DNA damage-repair pathways, and DNA-PK knock out cells accumulate nuclear survivin after UV irradiation (Asumen et al., 2010). Consistent with this, we identified DNA-PK and Ku70 as potential partners by Mass Spec analysis of in survivin co-immunoprecipitating proteins post-X-irradiation (Connell and Wheatley, unpublished), and similar data was published by (Capalbo et al., 2010). Whether survivin then aids in DNA repair per se remains to be determined, but early work from (Chakravarti et al., 2004) reported fewer comet tails post-IR in glioblastoma cell lines expressing survivin compared with control cells, indicating either less damage sustained or more efficient repair of DNA strand breaks.

Finally, could expression of survivin in the nucleus interfere with the cell's transcriptional programme? Although survivin has a zinc finger in its BIR domain, this fold is distinct from zinc rich domains found in many TFs, and accordingly survivin itself cannot bind directly to DNA (Klein et al., 2006). However, it has been suggested that survivin suppresses the cytokine activated transcription factor, STAT3, and that this association may be regulated acetylation of survivin at lysine, K129, in the carboxyl alpha helix (Wang et al., 2010). Although the consequences of this interaction are not clear at present, it is nevertheless intriguing that this could be one reason to eliminate survivin from the nucleus. In this regard it is important to note that significant new insight in the mitosis field has revealed that survivin interacts directly with the NH₂ tail of histone H3, which protrudes from the

nucleosome, and that this interaction is dependent upon phosphorylation of threonine 3 in histone H3's (Kelly et al., 2010; Wang et al., 2010). As this phosphorylation event is placed by the mitosis specific kinase, haspin, it is unclear whether such an interaction could occur in non-mitotic cells, however, indirect interactions in addition to direct binding between survivin and H2A also facilitates chromatin association (Kelly et al., 2010; Yamagishi et al., 2010), and borealin has been demonstrated to bind dsDNA directly in vitro (Klein et al., 2006). Hence, although not a transcription factor itself, it is indeed plausible that survivin could indirectly modulate transcription.

7. Clinical implications

Despite its clear importance in cancer, strategies targeting survivin for oncotherapeutic gain have been rather elusive. The question posed here is whether "nuclear survivin" offers a unique therapeutic window? Now that it has been established that nuclear export is essential for activity of survivin as a tumour promoter, one possibility proposed by Stauber and colleagues, is the development of molecular decoys that interfere with its export by antagonising the NES(s). Potentially this strategy could be used to eliminate survivin and (re)sensitise tumours to current cancer therapies (Knauer et al., 2007; Stauber et al., 2007). Intriguingly in 2005, Otto and co-workers used a HLA-A2 restricted survivin peptide to vaccinate patients with advanced, stage IV melanoma. Serendipitously, the epitope selected was a peptide within the central NES of survivin, 96-104 (Colnaghi et al., 2006). Whether this peptide interfered with nuclear exportation of survivin in vivo was not addressed, but the treatment was well tolerated by patients and importantly it enhanced tumour cell apoptosis and caused regression of metastatic lesions (Otto et al., 2005).

We have taken a different angle, endeavouring to exploit the ability of survivin to accelerate cells into S-phase for therapeutic gain (Suzuki et al., 2000). In brief we infected cells with oncolytic viruses engineered to reproduce only in cells with a defective pRB pathway, in this case ovarian cancer cells. As viruses reproduce in S-phase of the host cell cycle, when we compared efficacy of cell lysis post-infection between control and survivin-NLS expressing cells, a marked increase in cytotoxicity was observed, suggesting that nuclear survivin expression synergised with oncolytic virus potency, to effectively eliminate cancer cells (Connell et al., 2008b). These data from cultured cells are promising, and given that survivin is an essential protein it is likely that its oncotherapeutic potential will be realised in combination strategies like this, rather than as a target for a single agent.

8. Concluding remarks

Survivin is a prosurvival factor that can promote S-phase entry; is essential for mitosis; whose presence renders cells resistant to apoptosis; and that is expressed at high levels almost universally in tumours. As a disease of inappropriate cell growth, cancer may arise through deregulated proliferation or failure to die in response to death inducing stimuli, and the success of therapeutic interventions is likely to be a case of tipping the balance between prosurvival and proapoptotic factors. For all these reasons the case for survivin as a novel anti-cancer target is compelling. The ability to dissect the pleiotropic functions of the protein apart by changes in its subcellular distribution may provide opportunities for therapeutic intervention and tailored targeting strategies.

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