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CELL SCIENCE AT A GLANCE

SUBJECT COLLECTION: CELL BIOLOGY AND DISEASE

Survivin at a glance

Sally P. Wheatley[1,*] and Dario C. Altieri[2]

ABSTRACT

Survivin (also known as BIRC5) is an evolutionarily conserved eukaryotic protein that is essential for cell division and can inhibit cell death. Normally it is only expressed in actively proliferating cells, but is upregulated in most, if not all cancers; consequently, it has received significant attention as a potential oncotherapeutic target. In this Cell Science at a Glance article and accompanying poster, we summarise our knowledge of survivin 21 years on from its initial discovery. We describe the structure, expression and function of survivin, highlight its interactome and conclude by describing anti-survivin strategies being trialled.

KEY WORDS: Survivin, BIRC5, Cancer, Mitosis, Apoptosis

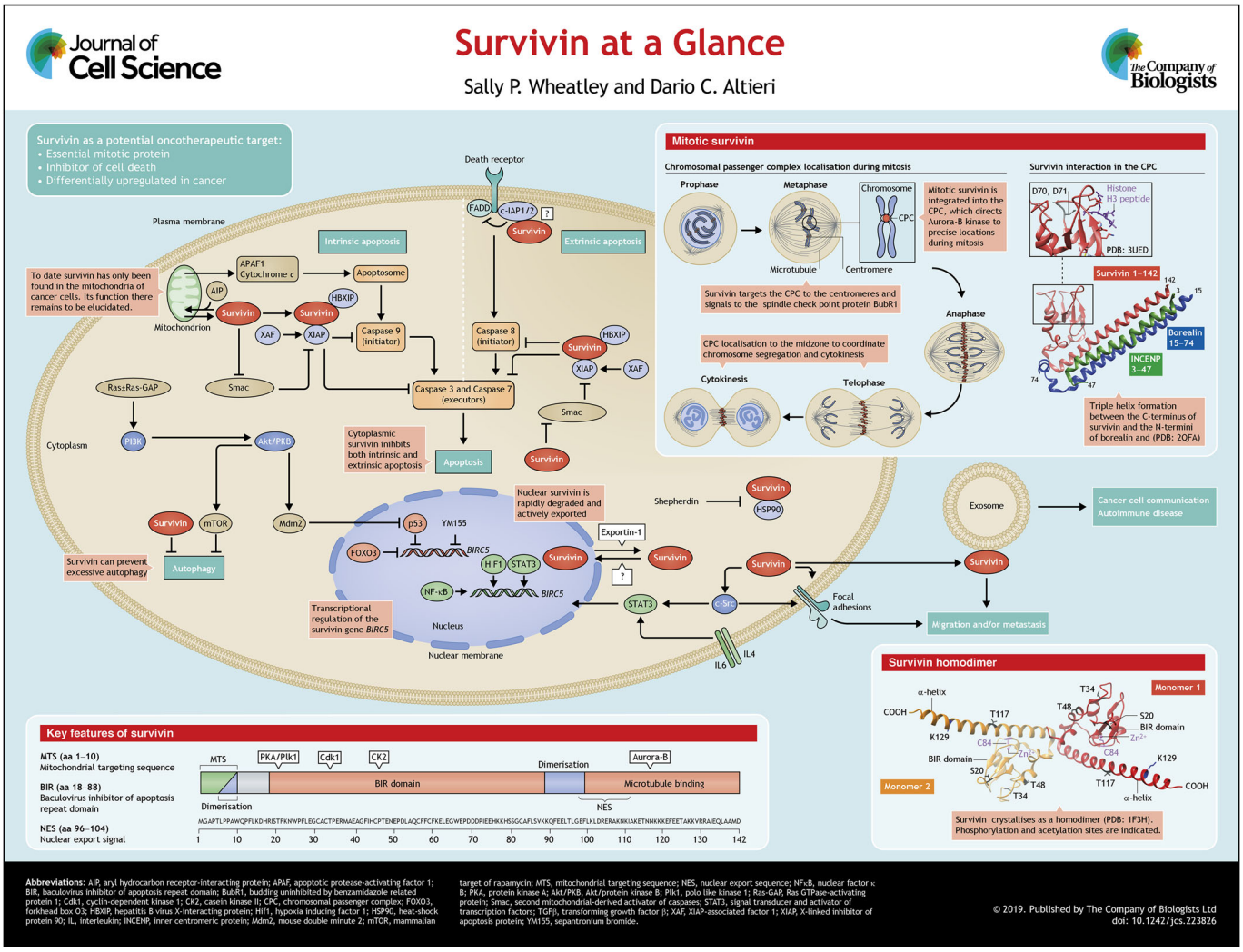
[1]Department of Biochemistry, School of Life Sciences, University of Nottingham, Nottingham NG7 2UH, UK. [2]The Wistar Institute Cancer Center, Philadelphia, PA 19104, USA.

*Author for correspondence (sally.wheatley@nottingham.ac.uk)

S.P.W., 0000-0002-9550-8979

Introduction

When survivin (BIRC5) was first described, its discovery sparked considerable interest from oncologists and cell biologists, an interest that persists today (Ambrosini et al., 1997). For oncologists seeking new anti-cancer targets, proteins that are required for cell proliferation feature high on their ‘most wanted’ list. Similarly appealing are proteins that interfere with programmed cell death (i.e. apoptosis), which is the intended response of tumour cells to traditional chemo- or radio-therapies. Therefore, as a protein that is



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both essential for mitosis and able to inhibit apoptosis, at first glance, survivin seemed a promising new target. Moreover, the most sought-after targets are those that are differentially expressed in cancer versus normal cells and, indeed, survivin is highly abundant in cancer (Velculescu et al., 1999), yet absent from most normal somatic cells. Thus in this respect too, it seemed an ideal candidate. Despite these desirable characteristics, rather disappointingly, a truly specific anti-survivin agent is yet to reach the clinic. Part of the challenge may be that survivin has no enzymatic activity of its own; instead, it achieves most of its tasks in association with other proteins and is probably best described as an adaptor protein that interacts with, or shuttles its partners to their destinations. This is certainly the case during mitosis, when it targets the chromosomal passenger complex (CPC) to the centromeres, thereby enabling aurora-B kinase to phosphorylate a number of proteins that ultimately ensure that the chromosomes are aligned properly before they are segregated at anaphase. Although it is less clear how survivin inhibits apoptosis, interactions with other members of the inhibitors of apoptosis (IAP) protein family (see Box 1), also appear to be key. In this Cell Science at a Glance article and accompanying poster, we aim to bring the reader up to date with the current understanding of this multi-tasking little protein.

Structure, domains and key partners

Survivin is a small protein [142 amino acids (aa); 16.5 kDa] with multifunctional domains (see poster). Its N-terminal two-thirds comprise a globular baculovirus inhibitor of apoptosis repeat (BIR) domain (aa 20–90), the integrity of which depends on a Zn^{2+} finger that is created by C57, C60, C84 and H77 (Li et al., 1999); this defines survivin as an IAP (see Box 1). The C-terminal third is an extended α-helix (98–142). Survivin crystallises as a homodimer; the two monomers interact via its central linker region (aa 90–102), assisted by N-terminal residues L6 and W10 (Verdecia et al., 2000).

Survivin uses the same interface to interact with its mitotic partner borealin (Jeyaprakash et al., 2007), and its C-terminus forms a triple helical bundle with the N-termini of borealin and inner centromere protein (INCENP) (Jeyaprakash et al., 2007). Together with aurora-B kinase, these proteins constitute the CPC, an essential mitotic complex. Survivin also has multiple non-mitotic partners, which influence its stability, and its role in the inhibition of apoptosis, subcellular localisation and pro-oncogenic signalling, as well as its other roles (see Table 1). Survivin undergoes several post-translational modifications, including phosphorylation by protein kinase A (PKA) and polo-like kinase (Plk1), (Dohi et al., 2007; Colnaghi and Wheatley, 2010); cyclin-dependent kinase 1 (Cdk1), (O'Connor et al., 2000; Barrett, et al., 2009), casein kinase II (CKII), (Barrett et al., 2011) and aurora-B kinase (Wheatley et al., 2007). It is also acetylated (Wang, H. et al., 2010b) and ubiquitylated (Vong et al., 2005).

Box 1. Apoptosis and IAPs

Apoptosis is the primary form of programmed cell death and depends on cysteine proteinases, called caspases, to disassemble the cell in a controlled manner (see poster). There are two apoptotic pathways: the intrinsic and extrinsic pathway. Upon receiving endogenous stress signals or irradiation, mitochondria initiate the intrinsic cascade through loss of the mitochondrial outer membrane potential and release of cytochrome *c* release; this causes activation of the initiator caspase, caspase 9. In contrast, the extrinsic pathway is mitochondrion-independent and is triggered by the binding of ligands to receptors at the cell surface, for instance, the TRAIL-bound TNF receptor (TRAIL is also known as TNFSF10), which activates caspase-8 via FADD, which can be inhibited by cIAP1 and cIAP2. After stimulation of the initiator caspases (caspase 8 or 9), both pathways converge on the effector caspases 3 and 7, which cause cellular demise by cleaving downstream macromolecules.

As the name suggests, the IAP family of proteins prevent this form of programmed cell death. Inclusion in the IAP family is based on the presence of at least one baculovirus inhibitor of apoptosis repeat domain (BIR), a globular fold that has been originally found in insect viruses. Humans have eight IAPs, of which survivin is the smallest. Initially thought to bind to and inhibit caspase activity directly, current views suggest that only the canonical member of this family, XIAP, can efficiently and directly inhibit caspases *in vivo* (reviewed in Lalaoui and Vaux, 2018). However, XIAP can interact with other IAPs, including survivin; this can improve its stability to augment the inhibitory effect of XIAP. For XIAP, both the linker between two adjacent BIR domains and the BIR domains themselves contribute to the prevention of apoptosis: the former disables the catalytic cysteine residue of the effector caspases, while the latter can prevent dimerisation of the initiator caspases, which is critical for their activation. Upstream factors such as Smac, which is released from the mitochondria upon apoptotic stimulation, can inhibit IAPs by binding to the BIR domain; this prevents Smac binding to its caspase target, and there is evidence to suggest that survivin might inhibit this inhibitor (Song et al., 2004).

Expression

Survivin is expressed during development (Uren et al., 2000) and in proliferating adult cells (Li et al., 1998). Apart from activated T lymphocytes (Leung et al., 2007), erythroblasts (Keerthivasan et al., 2012) and self-renewing stem cells (Martini et al., 2016), it is absent from adult cells. Human survivin is encoded by the *BIRC5* gene and located on the long arm of chromosome 17 (q25) (Ambrosini et al., 1997). It has a TATA-less promoter and four transcriptional elements: three cell cycle-dependent elements (CDEs), and a cell cycle homology region (CHR), which ensure its expression is minimal in G1 and maximal in mitosis (Li and Altieri, 1999). It is indirectly repressed by adenomatous polyposis coli protein (APC) (Zhang et al., 2001), retinoblastoma protein (pRB, also known as RB1) (Jiang et al., 2004) and phosphatase and tensin homologue (PTEN) and transforming growth factor β (TGFβ) (Martini et al., 2016) (Guha et al., 2009), and repressed directly by forkhead box O3 (FOXO3) (Hagenbuchner et al., 2012) and p53 (also known as TP53) (Hoffman et al., 2002) (see poster). Survivin expression is also under the influence of circadian rhythms (Siffroi-Fernandez et al., 2014), and is activated by many transcription factors, including hypoxia-inducing factor 1 (HIF1), nuclear factor κB cells (NFκB), signal transducer and activator of transcription factors (STATs), and β-catenin (for a full list, see Boidot et al., 2014).

BIRC5 has four exons and five introns, and encodes ten splice variants, seven with known function (Sah and Seniya, 2015). Although the isoform transcripts of survivin are frequently analysed in clinical studies, less information is available about the proteins; therefore, their significance as biomarkers in cancer remain unclear. The predominant wild-type form is referred to as survivin, after which 2β and ΔEx3 are the most common forms. Both deviate from survivin at the exon 2–exon 3 junction: 2β has a 26-aa insert that makes it pro-apoptotic; exon 3 is deleted in ΔEx3, causing a frameshift resulting in a different C-terminus. For further information regarding the different isoforms, the reader is referred to Sah and Seniya (2015).

Survivin is ubiquitylated and degraded by the 26S proteasome and has a half-life of 30 to 120 min. After mitosis, it is eliminated by midbody extrusion, and removal of any residual protein is mediated by the anaphase-promoting complex, an E3 ubiquitin ligase, that is activated by Cdc20 or Cdh1 (Connell, et al., 2008). Nuclear relocation of survivin reduces its half-life (Connell et al., 2008), and

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Table 1. Survivin-interacting proteins

Partner	Key domain/amino acids in survivin	Function	References
Aurora-B	D70, D71	Mitosis and stability	Wheatley et al., 2007
AIP	D142	Stability and mitochondrial targetting	Kang and Altieri, 2006
Beclin-1	ND	Autophagy?	Niu et al., 2010
Borealin	C-terminus	Mitosis	Jeyaprakash et al., 2007
Clathrin and EPS15	ND	Erythroblast enucleation	Keerthivasan et al., 2012
Exportin-1	NES	Nuclear export	Engelsma et al., 2007
Hsp90	BIR domain; aa 79–87	Stability	Plescia et al., 2005
HBXIP (Lamtor5)	BIR domain; T34	Apoptosis	Marusawa et al., 2003
Histone H3	D70, D71	Mitosis	Jeyaprakash et al., 2011
INCENP	aa 90–142	Mitosis and stability	Jeyaprakash et al., 2007
LC3	F61KEL	ND	Humphry and Wheatley, 2018
Ran-GTP	BIR domain; aa 55–79, E65	Mitosis, microtubule dynamics	Xia et al., 2008
Ras-GAP (SYNGAP1)	N-terminus	Oncogenesis	Temme et al., 2005
Smac (Diablo)	BIR domain; L64, L87	Apoptosis	Sun et al., 2005
c-Src	Aa 1–10	Adhesion and apoptosis	Dunajová et al., 2016
Survivin	F101, L102, L6, W10	ND	Verdecia et al., 2000
Tubulin	aa 99-142	Microtubule dynamics	Rosa et al., 2006
XIAP–XAF1 complex	BIR domain; aa 15–38	Apoptosis and stability	Arora et al., 2007

Where known the key sites of interaction on survivin are indicated, the function the interaction relates to, and a key reference(s), with priority given to structural data. ND, no data.

many of its interactions affect its stability. For instance, binding to X-linked inhibitor of apoptosis protein (XIAP) increases survivin turnover (Arora et al., 2007), whereas integration into the CPC stabilises it (Honda et al., 2003).

Localisation

Interphase

In interphase, survivin localises to the cytoplasm and/or the nucleus. The ratio between cytoplasmic and nuclear survivin has been assessed by many clinical researchers hoping to use it as a prognostic tool (Stauber et al., 2007). However, as with the survivin isoforms, data have been inconsistent, so the significance of this ratio remains uncertain. Survivin is trafficked out of the nucleus in an exportin-1-dependent manner (Stauber et al., 2006; Colnaghi et al., 2006). It has a centrally placed nuclear export sequence (NES) between the BIR domain and the C-terminal helix (Stauber et al., 2006; Colnaghi et al., 2006), which is masked by homodimerisation, and a bipartite NES in its C-terminus (Engelsma et al., 2007). While nuclear export is understood, how survivin enters the nucleus is not; it has no nuclear localisation signal and may depend on cofactor(s) to gain access (Villapol et al., 2008). Endogenous survivin is small enough to diffuse across the nuclear membrane, both as a monomer and a homodimer. However, the progressive nuclear accumulation of GFP–survivin, which is above the threshold size of diffusion, upon inhibition of exportin-1 (Connell, et al., 2008), suggests that it is actively imported (Colnaghi et al., 2006). Interestingly, Temme and co-workers noted that, in newly isolated fibroblasts, ectopically expressed survivin was nuclear but became progressively cytoplasmic with successive passages (Temme et al., 2005), which may depend on its association with heat-shock protein 90 (HSP90) and phosphorylation at T34 (Al-Khalaf and Aboussekhra, 2013). As age is one of the primary risk factors in cancer, this nuclear–cytoplasmic shift is intriguing.

Specifically in cancer cells, survivin is additionally detected in mitochondria (Dohi et al., 2004), and it is attractive to consider that mitochondrial survivin could be an ‘Achilles’ heel’ of cancer (Ausserlechner and Hagenbuchner, 2016). Note, however, that this pool of survivin, which is found in the inner mitochondrial membrane and matrix (Rivadeneira et al., 2015), is visually obscured by the cytoplasmic population, but can be readily detected by subcellular fractionation and immunoblotting, or by using nanobody trackers (Beghein et al., 2016). Mitochondrial import of survivin is directed through its proline-rich N-terminus (M^{1}GAPTLPPAW^{10}), which forms a canonical amphipathic α-helical mitochondrial targeting sequence (MTS) (Dunajová et al., 2016). Survivin can also be indirectly chaperoned into mitochondria by HSP90 and/or aryl hydrocarbon receptor-interacting protein (AIP) (Kang and Altieri, 2006). This pool increases with stress (Asumen et al., 2010), is released from the mitochondria into the cytosol in response to apoptotic stimuli and has enhanced anti-apoptotic activity compared to cytoplasmic survivin, the reason for which is unclear (Dohi et al., 2004).

Mitosis

In proliferating cells, survivin is first detected in G2 (Beardmore et al., 2004) when it targets the CPC to the centromeres through a direct interaction between its BIR-domain residues D70 and D71, and histone 3 that has been phosphorylated at T3 by haspin kinase (Jeyaprakash et al., 2011; Wang F. et al., 2010a; Kelly et al., 2010; Yamagishi et al., 2010). Several posttranslational modifications (PTMs) affect the centromeric association of survivin, most notably phosphorylation by aurora-B, and its ubiquitylation status, which is regulated by the de-ubiquitylating enzyme fat facet in mouse (FAM, also known as USP9X) (Vong et al., 2005). Survivin remains at the centromeres until the metaphase-anaphase transition, after which it travels to the midzone microtubules and the equatorial cortex, delineating the cleavage plane (see poster, mitotic survivin). How survivin is targeted to the midzone is unclear; however, this might occur through a direct association of its C-terminus with microtubules (Li et al., 1998). Its dynamic localisation during mitosis is regulated by all the key mitotic kinases (see poster).

Extracellular

Survivin has also been found on the surface of exosomes, which are constitutively secreted from cancer cells with secretion enhanced by oncotherapy; this suggests it may have prognostic potential in serum biopsies (Khan et al., 2011; Galbo et al., 2017). Interestingly, neighbouring cancer cells in culture can be coerced to proliferate and evade apoptosis by exosomally delivered survivin (Khan et al., 2011), demonstrating a role in cell–cell communication, which has already been reported in autoimmunity (see below).

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Cellular functions of survivin

Cell death

Survivin protects cells against apoptotic and autophagic death. Localisation within the cytoplasm is crucial to the anti-apoptotic activity of survivin, as nuclear relocation abrogates it (Knauer et al., 2006; Connell, et al., 2008). However, prior mitochondrial residence augments this activity (Dohi et al., 2004). While there is no doubt that caspase activity is reduced by survivin expression, in both homodimeric and monomeric states (Pavlyukov et al., 2011), unlike other IAPs, survivin only has a single BIR domain and does not bind to caspases at physiological concentrations. The current consensus is that survivin cooperates with XIAP and hepatitis B virus X-interacting protein (HBXIP, also known as LAMTOR5) in a complex with XIAP-associated factor 1 (XAF1) (Marusawa et al., 2003) to affect the interaction of XIAP with caspases or to augment the effect of other IAP family members, such as c-IAP1 or c-IAP2 (also known as BIRC2 and BIRC3, respectively), which act further upstream in the extrinsic apoptotic pathway (Verhagen et al., 2001). Survivin may also prevent the release of apoptotic protease-activating factor 1 (APAF1) from the mitochondria, or sequester the IAP inhibitor second mitochondrial-derived activator of caspases (Smac; also known as Diablo), away from other IAPs (Song et al., 2004).

To maintain homeostasis, a basal level of autophagy operates to remove defective organelles and misfolded proteins. In response to stress, such as nutrient depletion, autophagy is induced to enable short-term survival. However, as a catabolic recycling system, excessive autophagy ultimately kills a cell, which in a cancer context would be tumour suppressive. Cytokine treatment, which hyperactivates the protein kinase B (also called AKT1, herein denoted Akt/PKB), phosphoinositide 3-kinase (PI3K) signalling pathway and increases survivin expression, can inhibit autophagic death (Roca et al., 2008); conversely, pharmacological inhibition of survivin with sepantronium bromide (YM155) increases it (Wang et al., 2011). We recently discovered that survivin binds to the autophagic regulator microtubule-associated protein light chain 3B (LC3B, also known as MAP1LC3B) through a canonical LC3-interacting region in its BIR domain; however, this interaction did not have any effect on its inhibition of autophagy (Humphry and Wheatley, 2018). Whether survivin inhibits excessive autophagy in association with Beclin-1 (Niu et al., 2010), or other autophagic factors, remains to be determined.

Mitosis

By targeting the CPC to the centromeres during prometaphase, survivin helps to ensure that chromosomes are properly aligned prior to anaphase. It achieves this by communicating with the spindle checkpoint tension sensor BubR1 (‘budding uninhibited by benzamidazole-related protein 1’, also known as BUB1B in mammals) via aurora-B kinase, which detect and detach misoriented chromosomes, respectively, allowing the cell further attempts to attach chromosomes correctly. As noted above, during prometaphase, phosphorylation of survivin by aurora-B ensures that its association with the centromeres remains dynamic until all chromosomes have oriented (Wheatley et al., 2007, 2001; Lens et al., 2003; Carvalho et al., 2003). Survivin can also affect mitotic spindle assembly by dampening microtubule dynamics (Rosa et al., 2006; Cheung et al., 2009), a phenomenon that is mediated by Ran-GTP and TPX2 (Xia et al., 2008). Finally, survivin directs cytokinesis by delineating the cleavage plane prior to actomyosin recruitment. The coordination of mitosis and cytokinesis is an essential and conserved role of survivin in all eukaryotes from yeast (where the survivin homologue is known as Bir1) (Rajagopalan and Balasubramanian, 2002) to human. Accordingly, loss or depletion of survivin leads to prometaphase defects, cytokinesis failure, mitotic catastrophe and increased apoptosis in all model systems (Lens et al., 2003; Carvalho et al., 2003; Rajagopalan and Balasubramanian, 2002; Yue et al., 2008; Speliotes et al., 2000; Jones et al., 2000). Furthermore, the mouse knockout is embryonic lethal at 2.5 days post-coitum (Uren et al., 2000).

Mitochondria

Mitochondrial residence of survivin appears to be an exclusively cancer-associated phenomenon and can affect cellular metabolism; however, the current data are contradictory. For instance, in neuroblastoma cells, which have an additional copy of chromosome 17q (Islam et al., 2000), survivin increases glycolysis (Hagenbuchner et al., 2016), whereas in prostate cancer and glioblastoma cells with high survivin expression, oxidative phosphorylation is increased (Rivadeneira et al., 2015). The metabolic adaptability of cancer cells makes understanding this aspect of survivin biology particularly challenging. In addition, mitochondria are highly dynamic organelles that continuously fuse and undergo fission in order to ensure that their health is maintained and any damaged parts, such as mitochondrial (mt)DNA-harbouring reactive oxygen species (ROS)-induced lesions, are eliminated. Aside from metabolism, evidence is amassing that survivin regulates mitochondrial dynamics, but exactly how this is achieved also remains to be elucidated (Hagenbuchner et al., 2012).

Migration and angiogenesis

Linking ATP demand to migration, we witnessed that mitochondria are recruited to actively migrating areas of adherent cells overexpressing survivin (Rivadeneira et al., 2015). Moreover, survivin can alter focal adhesion dynamics by regulating c-Src activity, which may promote migration (Dunajová et al., 2016) (see poster). Interestingly, communication with c-Src may be bidirectional: using a temperature-sensitive c-Src expression system in MDCK (epithelial) cells, in which cell-cell and cell-matrix interactions were disrupted, ultimately increased survivin expression through T-cell factor–β-catenin signalling (Capra and Eskelinen, 2017). Survivin also has a pro-angiogenic role, as it is downstream of vascular endothelial growth factor (VEGF) and might also contribute to vascular remodelling through inhibition of apoptosis (Daly et al., 2004; reviewed in Sanhueza et al., 2015).

Stemness

In embryonic stem cells, survivin knockdown decreases the expression of the key transcription factors associated with pluripotency, namely octamer-binding transcription factor 4 (Oct4, also known as POU5F1) and Nanog (Mull et al., 2014), suggesting that it is involved in stemness. This has pathogenic and potentially therapeutic implications, because survivin appears to prevent aneuploidy and formation of micronuclei in pluripotent stem cells that undergo neurogenesis (Sartore et al., 2011), whereas pharmacological targeting of survivin is sufficient to abolish pluripotent stem cell and teratoma formation (Lee et al., 2013). Furthermore, survivin is expressed in stem cells and rapid-amplifying progenitor cells in the intestinal crypts, where it helps to maintain gut homeostasis (Martini et al., 2016).

Survivin is constitutively expressed in cancer stem cells (CSCs), a discrete cell population within a particular cancer that retains and/or regains stem-like qualities. For example, in acute myeloid leukaemia, CSCs are thought to drive the malignant state and to be responsible for resistance to and relapse after treatment (Zhang

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et al., 2015). In this case, transcriptional de-repression of survivin, mediated by mitogen-activated protein kinase (MAPK) signalling, and the transcription factors Sp1 (specificity protein 1) and c-Myc, promote its constitutive expression (Zhang et al., 2015). Siddarth and colleagues (2016) reported that survivin expression is linked to the pre-metastatic state of breast cancer stem cells. By noting changes after shRNA-mediated knockdown of survivin, they found that its expression was not only linked to self-renewal, but also to epithelial-to-mesenchymal transition (EMT), invasion and metastasis through alterations in WNT/β-catenin signalling (Siddharth et al., 2016).

Survivin signalling

The signalling aspect of survivin biology is complex and incompletely understood, and may also differ depending on the cellular context. Evidence to date suggests that activation of Akt/PKB and PI3K occurs upstream of many events that involve survivin. These kinases regulate numerous cellular processes, including cell cycle, metabolism, apoptosis, angiogenesis and autophagy, by instructing downstream transcription and translation factors that alter protein expression. Upstream of Akt/PKB and PI3K, are β-catenin, mammalian target of rapamycin (mTOR), the MAPK cascade and Ras. Immunologically, the interleukins IL4 and IL6 instruct the STAT family of transcription factors to promote survivin expression. Survivin signalling pathways are outlined in the poster.

Survivin in cancer and other diseases

Undoubtedly the main clinical interest in survivin is in cancer, as it is the fourth most upregulated mRNA in the human cancer transcriptome (Velculescu et al., 1999), and its expression has been correlated with increased tumour resistance to a broad range of chemotherapy agents, radiation insensitivity and poor patient prognosis. Derangement of its natural cycle of expression is due principally to transcriptional de-repression, which causes continuous synthesis throughout the cell cycle (Siffroi-Fernandez et al., 2014) and/or altered splicing (Antonacopoulou et al., 2011). Although many single-nucleotide polymorphisms (SNPs) have been found in its promoter, mutations within the gene coding region are rare, but one that has been reported is a lysine to glutamic acid mutation, K129E (Jang et al., 2008). When assessed in cultured cells, the K129E variant caused mitotic defects by decreasing the affinity of survivin to borealin (Aljaberi et al., 2014). Clearly, with roles in mitosis, apoptosis suppression, autophagy, migration, metabolism and angiogenesis, there are many routes through which survivin can promote tumour cell survival and cancer metastasis. In addition to cancer, survivin has been implicated in rheumatoid arthritis (Bokarewa et al., 2005; Mera et al., 2008) and multiple sclerosis (Hebb et al., 2008). In these autoimmune disorders, survivin is secreted and its cytokine-dependent expression correlates with reduced apoptosis and inflammation.

Therapeutic targeting

Despite the critical role of survivin as a universal cancer gene that is pivotal for disease maintenance, targeting of this pathway for novel therapeutics so far has garnered only limited success. Lacking intrinsic catalytic activity, and having few deep ‘pockets’ that are suitable to accommodate small-molecule antagonists, survivin joins the vast majority of cancer genes that are considered ‘undruggable’ in the conventional sense (Dang et al., 2018). Against this backdrop, the best-studied survivin suppressor is YM155. YM155 is not technically a direct survivin inhibitor, but instead predicted to shut off transcription of the *BIRC5* (survivin) gene, although this proposed mechanism is not universally accepted (Rauch et al., 2014). After encouraging phase I trials that showed manageable toxicity and hinted to clinical activity in heavily pre-treated patients (Tolcher et al., 2012), further clinical development of YM155 has been less successful and most combination regimens failed to meet their specified endpoints in different cancers, including advanced melanoma (Kudchadkar et al., 2015), HER2-negative metastatic breast cancer (Clemens et al., 2015), prostate cancer (Tolcher et al., 2012) and non-small cell lung cancer (Kelly et al., 2013). A potential exception may be advanced non-Hodgkin’s lymphoma; here, the combination of YM155 with rituximab, a therapeutic monoclonal antibody against the CD20 surface molecule expressed on B cells, appeared well-tolerated and produced durable responses (Papadopoulos et al., 2016) in patients with aggressive and relapsed non-Hodgkin’s lymphoma.

Alternative strategies to target the survivin pathway for novel cancer therapeutics continue to emerge. These include small molecule inhibitors of the survivin dimerisation interface (Qi et al., 2016), or adjacent cavities (Berezov et al., 2012), antibodies to a recently discovered cell surface pool of survivin (Fenstermaker et al., 2018), and survivin-directed short interfering RNA encapsulated in nanoparticles (Li et al., 2017). However, these approaches are still in their infancy and have yet to advance past preclinical evaluation.

Conversely, a third strategy aimed at generating survivin vaccines for cancer immunotherapy has successfully passed proof-of concept and has already produced encouraging results in the clinic (Kaneko et al., 2014). Specifically, several survivin-directed immunisation platforms have been developed that are well-tolerated in patients and give rise to robust immunological responses with initial evidence of clinical activity as both monotherapy or in combination in hard-to-treat malignancies; these are SurVaxM for malignant glioblastoma multiformis (Fenstermaker and Ciesielski, 2014) and the multi-epitope vaccine EMD640744 in solid tumours (Lennerz et al., 2014; Zhenjiang et al., 2018).

Conclusions and perspectives

In the wake of the 21st anniversary of its discovery, our knowledge of survivin has expanded exponentially, but we are yet to have a survivin-specific anti-cancer agent. However, now that we know survivin is a molecular collaborator extraordinaire, it is heartening that the development of drugs and peptides that target protein–protein interactions is gathering momentum (Dang et al., 2018). Incidentally, shepherdin, a competitive peptide that we developed to prevent survivin from binding to HSP90 has been used effectively in this capacity in the laboratory for several years (Plescia et al., 2005). Thus, now, with a relatively comprehensive understanding of survivin functions and a molecular inventory of its interactome, it seems that we are in a strong position to make headway in preventing this mischievous little protein from doing what it must.

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Competing interests

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Cell science at a glance

A high-resolution version of the poster and individual poster panels are available for downloading at http://jcs.biologists.org/lookup/doi/10.1242/jcs.223826.supplemental

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