Survivin is not only a death encounter but also a survival protein for invading tumor cells

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1. ABSTRACT

Cell proliferation and cell death pathways meet at a pivotal crossroad, crucial to maintain normal homeostasis and to eliminate dangerous cells before they start dividing. Survivin (SVV) is an intriguing and fascinating protein at this crossroad that interfaces life and death, through its dual role in facilitating cell division and encountering apoptosis. SVV’s prominent expression in essentially all human malignancies, and low or no expression in most normal tissues, suggests that it would be an ideal target for cancer-directed therapy. However, SVV has been recently described as a target for fine tuning by alternative splicing mechanism generating five defined splice variants and a number of other uncharacterized/bizarre isoforms. This diversity indicates that SVV, in addition to its known functions in tumorogenesis, angiogenesis and cardiovascular diseases, might be associated with other unknown functions. Intriguingly, new accumulating evidence from our own work and others, suggest a novel role for SVV in the mechanisms of tumor invasion and metastasis. The SVV pathway has now provided tangible opportunities for targeted, rational cancer therapy. It is therefore an attractive and promising therapeutic target not only for cancer but also for other diseases. Although a number of studies utilizing SVV as an anti-cancer strategy are well underway, further investigation into the exact molecular interactions underpinning its functions is critical for the success of such trials. Impeding development of safe and effective SVV antagonists for clinical use is due to a lack of understanding the molecular mechanisms by which SVV differentially affects apoptosis and cell division in both normal and malignant cells. In this report, in addition to reviewing the SVV known functions, we discuss the newly proposed mechanisms by which SVV might serve as a survival tool for invading tumor cells.
2. INTRODUCTION

A delicate balance between cell proliferation and cell death is required to maintain cell and tissue homeostasis and thereby preventing the development of a variety of pathologic outcomes, including cancer and vascular diseases. Deregulation of apoptosis during homeostasis is considered as a critical step for cancer development and progression, although the underlying mechanisms are not yet fully understood. In addition to anti-apoptotic and pro-apoptotic factors including Bcl-2 protein family, the inhibitor of apoptosis proteins (IAP) are a family of recently discovered proteins. Eight human IAP family members have been identified so far, characterized by a molecular signature consisting of one to three copies of a ~70-amino acid zinc finger fold designated Baculovirus IAP repeat (BIR), which is conserved from yeast to humans (reviewed in ref. 1). Survivin (SVV) is a prototype molecule, countering cell death and facilitating various aspects of cell division. It has been studied extensively and forms the basis of the current knowledge and characterization of IAP family (1-2). It was identified in 1997 by hybridization screening of a human P1 genomic library with the cDNA of factor Xα receptor EPR-1 (3). It is a centromere binding passenger protein (4), which is onco-foetally expressed and is required for the successful completion of the cell cycle. Compared to other IAP members, SVV is unique with three distinctive features: 1) its structure contains a single baculovirus IAP repeat (BIR) domain combined with a COOH-terminal alpha-helix coiled-coil domain (observed to inhibit caspases); 2) it is the only IAP tightly regulated during cell cycle program and 3) it is virtually undetectable in most normal adult tissues, but dramatically over expressed in many human tumors, suggesting that reactivation of the SVV gene frequently occurs in cancers (5-6).

The dual role of SVV, in countering apoptosis and facilitating cell division mechanisms, has been extensively explored in cancer cells (reviewed in Ref. 1). In fact, the BIR motif of IAPs is cysteine and histidine rich and is thought to directly bind certain caspases (7) and consequently inactivate the intrinsic apoptosis pathway. However, this may not be its only function, as other BIR containing proteins are not implicated in apoptosis control such as Ac-IAP (7). Some IAPs also rely on a caspase recruitment domain (CARD) and a carboxy-terminal RING finger motif, neither of which when removed are essential for apoptosis inhibition (7-8). Evidence from the deletion of the RING domain in c-IAP2 suggests its crucial role in TNF-α-induced apoptosis mediated by NFκB activation (9). In addition to its role in cancer development (5, 9) and cardiovascular diseases (reviewed in 1), accumulating evidence from our laboratory and others suggests a role for SVV and its variants in the process of cell invasion/metastasis (10-14). This review will discuss these mechanisms and provide an update of our current understanding of the multifunction facets of SVV. As our knowledge of SVV’s action develops, its remarkable properties are being exploited as already trials have been undertaken. These experiments target specific mutations in the SVV gene that theoretically will result in the preferential demise of transformed cells whilst having minimal toxic effect on normal cells.

3. SURVIVIN: STRUCTURE AND LOCALIZATION

The human SVV gene, spanning 14.7 kb on chromosome 17q25, codes for a 16.5-kDa protein of 142 amino acids (2). SVV gene has been recently identified to undergo alternative splicing mechanism that generates a number of different SVV splice variant transcripts encoding proteins (Figure 1), which have unique subcellular localizations, suggesting a fine tuning of SVV actions (1-2). To date, five SVV splice variants have been described (2). Intriguingly, new and yet to be characterized SVV variants have been identified from EST databases (2). The presence of these SVV splice variants indicates that...
Ex3 protein by ubiquitin tagging. SVV-Ex3 during cell cycle
Ex3 may have functions and translocation of SVV during carcinogenesis, indicating that mechanism for its role in carcinogenesis and tumor localization of SVV may constitute an important regulatory midzone (23), to centrosomes (3, 24) or to kinetochores (22). On the subcellular level, it was shown that SVV-2B is a pro-apoptotic protein (17), suggesting that it might be a naturally occurring antagonist of anti-apoptotic SVV and SVV-Ex3, possibly by competitive binding to common interaction partners, as reported for SVV and SVV-2B interactions with polymerized tubulin (18); 4) SVV-3B: results from the introduction of exon 3B resulting in a frame shift and premature termination of the protein. No function has yet been described for SVV-3B; and 5) SVV-2α: is a SVV recently identified and characterized. The transcript consists of exon 1, exon 2, and a 3′197 bp region of intron 2 (Figure 1). Acquisition of a new in-frame stop codon within intron 2 results in an open reading frame of 225 nucleotides, predicting a truncated 74 amino acid protein. SVV 2α, expressed at high levels in many malignant cell lines and primary tumors. It can physically interact with SVV and disrupt its anti-apoptotic functions in malignant cells, suggesting its importance as a therapeutic tool in sensitizing chemo-resistant tumor cells to chemotherapy.

SVV is usually located in the cytoplasm and is associated with poor prognosis (19). However, nuclear localization of SVV has been described in 80% of patients with esophageal squamous cell carcinoma (20-21). Grabowski et al. (2003), were the first to show a translocation of SVV during carcinogenesis, indicating that localization of SVV may constitute an important regulatory mechanism for its role in carcinogenesis and tumor progression (20). The ratio of cytosolic vs. nuclear SVV is 6:1 (22). On the subcellular level, it was shown that SVV binds to microtubules of the mitotic spindle and the midzone (23), to centrosomes (3, 24) or to kinetochores (25). The diversity of subcellular localization might be related to the analysis of different SVV fusion proteins or use of SVV antibodies recognizing distinct epitopes (22, 24) but also from differences in Thr34 phosphorylation (22) or cell culture conditions.

The cytoplasmic co-localization of anti-apoptotic SVV and pro-apoptotic SVV-2B might regulate SVV actions in precise manner. In contrast, the anti-apoptotic SVV-Ex3 exhibited a preferential localization in the nuclear compartment from late G1 to G2 phase, suggesting a regulatory role for SVV-Ex3 during cell cycle progression. SVV-2B and Ex3 may have functions and molecular interaction partners different from SVV in distinct phases of the cell cycle. Further studies using specific antibodies for each isoform are necessary to elucidate the regulatory interactions of different SVV variants under physiological conditions and subsequently their differential functions.

4. REGULATION OF SURVIVIN EXPRESSION

SVV has been described as an oncofetal protein (26). Northern blot analysis and in situ hybridization evidence have demonstrated selective high expression of SVV transcripts in fetal tissues in comparison to an almost ubiquitous absence in normal differentiated adult tissues, and a dramatic return to fetal levels in tumor tissues as well as in some premalignant conditions such as actinic keratoses (27). These specific expression patterns suggest that SVV plays a distinct role in development, tumorigenesis and tumor cell viability.

To date, little is known about the mechanisms regulating SVV gene expression. Zhang et al. have reported that wild type APC can down-regulate SVV gene expression via APC/β-catenin/TCF-4 signaling pathway (28). The tumor suppressor p53 gene has been found to bind the SVV promoter and cause a strict reduction in its expression, while several p53 mutants had no effect, suggesting an interference with the E2-F mediated transactivator and/or histone acetylation of the promoter (29). Conversely, SVV over expression inhibits p53 dependent apoptosis (30). Together these observations imply a p53/SVV antagonistic relationship. Members of the Rb/E2F pathway can also regulate SVV gene expression (31). On the other hand, it has been found that both pRB and p130 can interact with the SVV promoter and repress SVV transcription. Also E2F activators such as E2F1, E2F2, and E2F3 can bind the SVV promoter and induce SVV transcription (31). In a recent study, SVV was identified as a direct downstream target gene of Stat3 in human breast cancer cells that is critical for their survival in culture (32). Recently, Xia et al. using genetic and pharmacologic approaches to block ErbB2 signaling, have showed that ErbB2 regulates SVV protein expression in ErbB2-overexpressing breast cancer cells (33).

5. DUAL ACTION OF SURVIVIN

At subcellular level, SVV is localized in the cytoplasm and the nucleus (19-21). This is consistent with its dual regulation of cell viability and cell division. The nuclear SVV might be involved in promoting cell proliferation in most (if not all) cases whereas the cytoplasmic SVV may participate in controlling cell survival but not cell proliferation. In addition, SVV has a number of splicing variants, which may differ in their subcellular localization and functions with respect to cell survival and cell division (13).

5.1. Survivin and apoptosis

Apoptosis or programmed cell death is an essential process within the body that regulates cellular numbers and protects the body of potentially hazardous cells. Apoptosis mechanisms have been a target area for a
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number of studies due to the fact that loss of homeostasis between cell proliferation and cell death can result in a number of pathologies. This is often the case in cancer where imbalance in this process results in increased transformed cell viability and possible immortalization. Accumulating evidence indicate that SVV controls both apoptosis and cell division during mitosis (1). SVV’s anti-apoptotic effect was initially identified when overexpression of SVV in a mouse IL-3-dependent pre-B cell line, BaF3, inhibited apoptosis induced by deprivation of interleukin-3 (34). It must be emphasized that the majority of the current studies indicated that inhibition of apoptosis by SVV is during mitosis and appears to be involved in a novel mitotic spindle assembly checkpoint.

Apoptosis can be explained basically through two main interconnecting caspase cascades in mammalian cells (extrinsic and intrinsic), although these are not mutually exclusive. The extrinsic pathway is activated following ligation of death receptors at the cell surface to activate caspase 8. For example, this pathway is important in the control of inflammation through stimulation by tumor necrosis factor-α (TNF-α). However, the intrinsic pathway is affected following exposure to a variety of death stimuli resulting in the breakdown of the mitochondrial membrane and the release of cytochrome c and SMAC/DIABLO protein (35), leading to activation of caspase-9. This pathway is triggered through intracellular and environmental DNA damaging agents, most notably targeting the dysfunction of the p53 gene (36). The major interaction between these two pathways occurs in the initial stages as a consequence of decreased caspase-8 cleavage. A Bcl-2 family member counteracts the depletion by initiating the intrinsic pathway through direct action on the mitochondria membrane (35). Activation of terminal effectors during apoptosis, caspasess-1 and 3 in particular, links the two pathways and is responsible for the cleavage of critical cellular substrates (i.e. ADP-ribose and lamins) resulting in dramatic morphological changes of apoptosis, including cytoplasmic shrinkage and formation of apoptotic bodies.

Although the contribution of SVV to apoptosis inhibition has in the past been controversial, accumulating data from several studies indicate a role for SVV in cell survival. Observations of SVV expression provide evidence that it promotes cell viability by interfering with the initiation and/or amplification of the intrinsic caspase cascade. This occurs through SVV binding and inhibiting procaspase-9 action if associated with the cytochrome C/Apaf-1 (apoptosis activating factor-1) complex and inhibiting caspase-3 and 7, respectively (23). SVV may also indirectly inhibit the extrinsic pathway through its action on caspase-3 and 7, however it has not been found to have an effect on caspase-8 (8). Another theory of SVV’s indirect action on caspases is the association of SVV with cdk4 resulting in a release of p21Cip1/Waf1 that in turn interacts with procaspase-3 to suppress Fas mediated cell death (37).

The study of mutant forms of SVV provides further evidence of SVV’s role as an apoptosis inhibitor. The BIR/ zinc binding mutation Cys84-Ala (C84A) in SVV resulted in apoptosis (38) but retained SVV’s ability to associate with microtubules. Over expression of the mutant increased caspase activity predominately occurring at G2/M, which suggests that both a viable BIR motif and microtubule binding are essential for SVV’s anti-apoptotic functions, and that the lack of apoptosis is triggered by a breakdown in a yet unknown G2/M checkpoint (8). Another carefully studied SVV mutation is Thr34Ala (T34A) that abolishes a phosphorylation site for p34cdc2 cyclin B1, which thought to be essential for caspase-9 inhibition (39-40). Adenoviral transduction of cells with T34A SVV mutant advocates that phosphorylation on Thr34 may regulate apoptosis at cell division via an interaction with caspase-9 (40).

5.2. Survivin and cell cycle regulation

SVV is a mitotic gene, whose expression at cell division is tightly regulated at both RNA and protein levels, in both normal and tumor cell lines (1, 21, 23, 41-42). After its expression at mitosis, SVV localizes to various components of the mitotic apparatus (22-23, 25), to potentially recruit and regulate the function of other proteins like Aurora B kinase involved in central spindle formation and cytokinesis (24). The maximal level of expression has been detected in the G2/M phase of mitosis in normal proliferating cells (41) and a significant reduction in activity seen in G1 phase after cell cycle arrest (41). The G1 transcriptional repressor elements CDE (downstream of the transcriptional start site) and proximal CHR have been demonstrated to control cell-cycle progression (23). SVV localizes to the mitotic spindles and remains present with the mid-body until just before cytokinesis (36). SVV’s over expression results in acceleration of S phase shift, resistance to G1 arrest, and cdk-2/cyclin E activation and retinoblastoma (Rb) phosphorylation (37).

SVV exhibits a cycle-regulated pattern of expression during the G2/M phase of the cell cycle (23) and behaves as a typical chromosome passenger protein that associates to centromeres from late prophase to metaphase (3). Using human cells depleted of SVV, Lens et al. have demonstrated that SVV is essential for chromosome alignment, sister chromatid segregation and cytokinesis (44). They have provided evidence that SVV is required for a sustained checkpoint arrest in response to lack of tension at the kinetochore in a SVV-dependent mechanism recruiting Aurora B protein to the inner centromere, while a SVV-independent mechanism involving Mad2-BubR1 complex is recruited to the kinetochore. It has been reported that disruption of SVV/microtubule interactions resulted in loss of SVV’s anti-apoptosis function and increased caspase-3 activity, suggesting that SVV may counteract a default induction of apoptosis and favors aberrant progression of transformed cells through G2/M phase (23). SVV has been proven to be an important regulator of the cell cycle as anti-sense targeting and dominant negative mutations in this gene resulted in terminal stage defects in cell division (8, 22) such as incomplete cytokinesis, polyploidy and multinucleated cells (36). Antibody targeting of SVV in vitro caused similar
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dysfunctional phenotype (45). Further evidence states intracellular antibody targeting of SVV does not affect cytokinesis but causes multipolar mitotic spindle formation (22). An in vivo demonstration of SVV’s role in the cell cycle has been observed in mice embryos, where mortality ensued by embryonic day 4.5 when both SVV alleles were functionally damaged (3).

6. SURVIVIN AND CARCINOGENESIS

Deregulation of apoptosis and cell cycle mechanisms are key processes involved in carcinogenesis by abnormally prolonging cell survival, facilitating the accumulation of transforming mutations and promoting resistance to immune surveillance. As already discussed (1), the expression of SVV is elevated in tumors, and it is now considered as the fourth major transcriptome demonstrated in human tumors. SVV is over expressed in tumors and correlates with more aggressive cancers, poor prognosis, more frequent recurrence rates, and increased resistance to therapies (4-5, 27, 35, 45). SVV has been found in at least 60 cancer cell lines, including those derived from colorectal cancers (46), neuroblastomas (47), and breast carcinomas (33, 48). Nuclear SVV expression, considered as a favorable prognostic factor, was detected in 82% gastric cancer cases, 70% cases of hepatocellular carcinoma, 80% cases of esophageal squamous cell carcinoma (3), 74% cases of ovarian carcinoma (8), 67% cases of non-small cell lung cancer (83% in the cytoplasmic and 44% in both), and in 45% cases of cholangiocarcinoma (54% cases had cytoplasmic SVV).

Originally, SVV was proposed to be over expressed in cancer because the increased levels simply correlated with tumor cellular proliferation, however further studies dismiss this opinion as SVV expression remains almost constant regardless of the tumor mitotic index (49). More recent studies suggest that demethylation of the SVV gene may be an important regulator of SVV expression in ovarian tumors (50). SVV expression is silenced in normal ovarian tissue through methylation of CpG sites in exon 1 (sites that are associated with the facilitation of structural changes in chromosomes), however SVV was observed to be transcriptionally active following demethylation of the gene (4). The action of dMTase is highly tumor specific and present in both initial and progressive tumor grades suggesting that this event occurs early in the transition (50); if SVV expression is regulated by this enzyme it may explain why SVV is over expressed early in cancers.

SVV may also be linked to mutations in the adenomatous polyposis coli (APC) gene, an initiating event in the progression of colon cancer model that was developed by Vogelstein in 1988. Results from recent study suggest that the wild type APC may limit population size of stem and other proliferative cells in the normal human colonic epithelium by decreasing SVV expression and increasing apoptosis rate, but inactivation of APC may allow expansion of these populations, thereby initiating tumorigenesis (28).

7. ROLE OF SURVIVIN IN TUMOUR INVASION & METASTASIS

SVV is over expressed in high grade, invasive tumors as discussed above, suggesting that it may play a role in metastasis (Figure 2). SVV has been particularly linked with an invasive phenotype in gastric (51), esophageal (52), and ovarian (11) cancers as well as endometriosis (53). SVV may provide invading cells with an enhanced survival capability through which they can evade the body’s immune responses and physical barriers presented during the process of tumor invasion. This process involves at least three major components including cytokines/growth factors, adhesion molecules and proteinases. Matrix metalloproteinases (MMP) are proteolytic enzymes capable of degrading the components of the extracellular matrix (ECM) and evidence suggests that they play a significant role in tumor invasion. Observations from recent studies imply that up regulation of SVV and MMPs may cooperate and contribute to tumor cell survival and invasion in endometriotic tissues (53). Yoshida et al (2001) have progressed this relationship further and proposed an association between SVV over expression and MMP-2 resulting in the breakdown of essential components of the ECM (11). Preliminary work from our laboratory suggests another possibility for this emerging hypothesis where we propose the involvement of the phosphatidylinositol 3-kinase/Akt/protein kinase B (PI3-K/Akt/PKB) signaling pathway (Figure 2). This pathway is considered to play an essential role in the survival response induced by a variety of growth factors, hyaluronan (HA)-CD44 adhesion receptor interaction and oncogenic transformation (54). Results from our laboratory support that increased CD44 expression in response to EGF stimulation plays a significant role in the process of tumor invasion (55). Ghatak et al (56) have found that perturbation of HA-CD44 binding leads to suppression of the PI3-K/Akt cell survival pathway and consequently to inhibition of anchorage-independent growth in culture and tumor growth in vivo. Also, it has been reported that upon binding to the CD44 receptor, the wild-type osteopontin but not the inactive mutant induces activation of PI3-K/Akt pathway (54). Findings from previous study support the hypothesis that APC suppresses SVV expression via TCF-4/ß-catenin signaling modulating the transcription of several genes including CD44 (53). Interestingly, RasP13-K and RasRaf/MEKMAPK can up regulate SVV, since chemical inhibition of both signaling cascades abolished SVV expression (57). Also, both angiopoietin-1 (58) and vascular endothelial growth factor (VEGF) (59) can stimulate SVV expression via the PI3-K/Akt/PKB pathway (Figure 2). SVV expression mediated by VEGF also preserves microtubule structural integrity. More interestingly, our ongoing work suggests that SVV is a key component of the HA-CD44 pathway mediating tumor cell invasion/metastasis (data not shown).

8. POTENTIAL THERAPIES AND FUTURE CONSIDERATIONS

Despite its relatively recent discovery in 1997, SVV has attracted considerable interest of the scientific
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community from several viewpoints of biomedical sciences. Its dual implication in cell death regulation and mitotic progression, its deep wiring with fundamental checkpoints of genomic fidelity and its transcriptional regulation by a plethora of signaling pathways have positioned SVV at the crossroad of several fields of investigation in biology. More interestingly, the recent knowledge of its diverse splice variants and multi-functions distinguishes SVV as an attractive target and promising lead, not only for cancer but also for therapy of cardiovascular diseases. A number of cancer therapies have been designed based on the following strategies (reviewed in references 1 and 2): (i) inhibition of SVV expression using SVV antisense oligonucleotides, SVV antisense expression vectors, RNA interference (RNAi: siRNA or shRNA), ribozymes, triplex DNA formation, and anti-cancer agents (e.g. vincristine, flavopiridol...), individually or in combination; (ii) suppression of SVV function using SVV-dominant negative mutants (e.g. T34A or C85A mutants of SVV), pharmacological inhibitors, or SVV peptidomimetic, individually or in combination; (iii) immunotherapy using SVV cDNA, RNA, protein or peptides; and (iv) applications of the SVV promoter as a vehicle for cancer-specific expression of cytotoxic genes.

Survivin is also implicated in angiogenesis and cardiovascular diseases. While, its level is barely detectable in endothelial cells (EC), SVV expression can be induced (10 to 20 fold) by vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) (60). In addition, excessive apoptosis in EC was shown to be involved in many EC-associated diseases including atherosclerosis (61). Since SVV is up-regulated in cancer, the cancer therapies targeting SVV may, not only have advantages over other therapeutic targets in inducing tumor cell death and regression of tumor vascular network simultaneously, but might also be useful in the treatment of cardiovascular diseases. More efforts appear to be required for the delineation of molecular mechanisms of the role of SVV in cancer development and progression. Nevertheless, there is ample data indicating that SVV and its variants may have a differential role in tumorigenesis and cancer development. Understanding the molecular mechanisms that underpin the complexity of SVV network pathway including its diverse splice variants is the key to the design of appropriate and precise therapies for cancer and cardiovascular diseases.

9. CONCLUSION

Even though a vast array of information on SVV has been revealed since its discovery, further research is required to elucidate unexplained or controversial aspects of SVV. For example, SVV is more highly expressed in tumors than any of the other IAP family members but is not considered to be the most potent IAP. This suggests that SVV may play a more elusive role in cancer progression than is known at present. Whether the explanation lies in SVV’s cell cycle regulated expression or through its potential involvement in the process of tumor dissemination is unknown. More interestingly, it is of no surprise that SVV is involved in both cancer and cardiovascular diseases, as they share many similarities (62). Impeding development of safe and effective SVV antagonists for clinical use is a lack of understanding of the molecular mechanisms by which SVV differentially affects apoptosis and cell division, in normal and malignant cells. Enhanced understanding of SVV’s regulatory functions may facilitate the design of appropriate and effective therapeutic strategies that can be applied not only to cancer but also in the treatment of vascular diseases.

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