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Survivin as a Cancer Vaccine Target

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Abstract

Survivin expression is associated with a poor prognosis in many cancers. While survivin is being studied as a potentially important target for cancer therapy, its many biological functions in both normal and cancerous cells remain to be fully elucidated. There are at least six specific survivin splice variants that have been identified to date which appear to be self-regulating and may have distinct functions. Several survivin peptide vaccines are currently under development by different groups. Survivin vaccine strategies for the most part have focused upon particular regional epitopes of the molecule that are bound by MHC class I and can lead to a cytotoxic T cell response. Immunotherapy targeting survivin is still at an early stage of development; however, several agents are progressing through early phase clinical trials. Recent studies using SurVaxM, a multi-epitope cryptic peptide, survivin, mimic show specific CD8+ T cell responses, as well as specific CD4+ T cell stimulation. Currently SurVaxM is in Phase I clinical trials designed to study its safety, tolerability and immunological effects in patients with survivin-positive recurrent malignant gliomas and multiple myeloma.

Keywords: Survivin; Immunotherapy; Peptide; Vaccine; Apoptosis

Survivin

Survivin is an 16.5 kDa intracellular protein that mediates a number of anti-apoptotic and oncogenic effects [1]. Survivin belongs to the inhibitor of apoptosis protein (IAP) family [2,3]. It acts in concert with the mitotic spindle apparatus to regulate cell division [4] and localizes to the spindle microtubule organizing center (MTOC) during the G2/M phase of the cell cycle [2,3,5]. Survivin has also been shown to modulate the function of a number of terminal effector cell death proteases (caspases) leading to an inhibition of apoptosis [3,6-8]. Survivin expression is associated with a poor prognosis in many cancers [9,10]. While survivin is being studied as a potentially important target for cancer therapy, its many biological functions in both normal and cancerous cells remain to be fully elucidated.

Survivin appears to function mainly as an anti-apoptotic molecule and its ability to interfere with p53 is one of its most studied molecular action [11-13]. However, the presence of survivin in the nucleus [14]; its interaction with the mitotic spindle [5]; its secondary localization inside mitochondria [15]; its presence in exosomes in plasma [16] observed exosomal release [17]; and the existence of circulating survivin-encoding mRNA [18,19]; and the existence of a many alternative mRNA splice variants all paint a complex picture of the molecule's possible actions. Although expressed during fetal development [1], survivin is rarely detectable in the normal tissues of adult organisms [20]. The cells of many different forms of cancer express survivin [1] and in some cases expression is related to tumor grade [9,10,21]. Survivin expression in tumors is associated with a high rate of disease recurrence and resistance to therapy, and it confers significant survival advantage to tumor cells [22,23].

Survivin Cell Biology and Molecular Mechanisms

Due to its relatively specific expression in cancer cells, survivin presents a therapeutic target. Immunotherapy by active immunization is one promising means by which survivin-expressing cancer cells can be targeted. Vaccines directed against an intracellular protein, such as survivin, target the post-proteasomal processed, fragments of the molecule which are presented at the cell surface by MHC class I or class II molecules [4,21,24-26]. Consequently, the immune system may recognize survivin's processed molecular fragments and produce a cytotoxic cellular response to those tumor cells. However, it is the essential nature of survivin's action that could make it a particularly good immunotherapeutic target [27,28]. One of the ways a tumor cell may evade immune recognition is through down-regulation of the target protein. In the case of survivin, this should naturally lead to activation of the apoptotic pathway [29]. While the action of exosomal survivin is not well understood, it may mediate cellular signaling in some way [16,17]. Thus, in addition to producing a direct cell-mediated antitumor effect, active specific vaccination against survivin could lead to antibody-mediated interference with these actions.

Another interesting feature of survivin resides with the number of splice variants that have been identified to date. There are at least six specific survivin variants which appear to be self-regulating and which may have distinct functions [30,31]. The survivin splice variants are generated through combinations of exons 1-4 with two alternate exons 2B and 3B (Figure 1) [30-32]. Survivin-2B and survivin-ΔEx3 are two well-studied forms [33-35]. Survivin-2B is formed by the addition of

an alternate exon 2 and survivin-ΔEx3 is an exon 3 deletion variant which results in a truncated protein due to a frame shifted stop codon [30]. A high ratio of survivin-ΔEx3 to wild-type survivin has been identified in aggressive cancers; whereas, when survivin-2B is predominant over wild-type survivin, a reduced anti-apoptotic potential is observed [33,36-42]. High expression of survivin-ΔEx3 has also been correlated with high proliferative activity and tumor recurrence potential, while survivin-2B tends to be associated with a lower rate of tumor recurrence [34,43,44]. Splice variants may also affect the cellular localization of the survivin protein [14,45]. Survivin-2B preferentially localizes to the cytoplasm, while survivin-ΔEx3 preferentially localizes to the nucleus [14,46]. Interestingly, high nuclear survivin expression is related to laryngeal cancer recurrence [47]. Wild-type survivin and survivin-ΔEx3 have also been observed to interact within the mitochondria [36]. The subcellular localization of survivin can vary in some cancers. Illustrative of this, three cases of glioblastoma multiforme are shown in Figure 2.

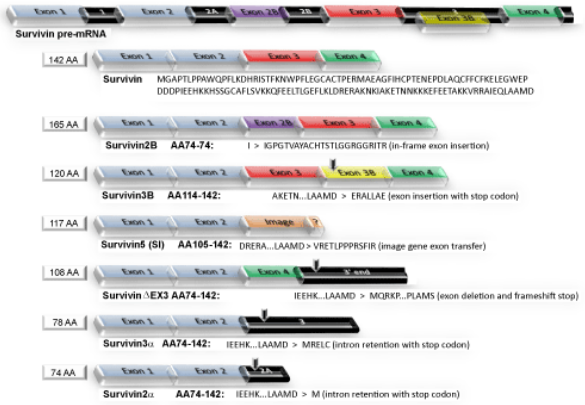

Figure 1: Survivin splice variants described to date. Depiction of survivin pre-mRNA and its derived splice variants. Amino acid sequence alterations from the primary survivin transcript are shown below each splice variant exon structure. Information derived from O15392 (BIRC5_HUMAN) UniProt database [31] and [32].

Survivin-2α has been shown to attenuate the action of wild-type survivin and to co-localize with it [48]. While it retains anti-apoptotic function, survivin-3B does not appear to be associated with the G2/M phase, suggesting different regulatory effects of the two molecular forms [49]. Moreover, depletion of cellular survivin does not lead to complementation by the splice variants [50].

Insulin-like growth factor-1 (IGF-1) is able to shift the survivin pre-mRNA splicing program from production of survivin-2B to that of wild-type survivin, thus promoting the cell survival action of IGF-1 [51]. Cumulatively, these observations demonstrate the multifaceted nature of survivin biology and raise the possibility that in addition to the wild-type survivin, the unique survivin epitopes present in these forms may be specifically targetable via active immunotherapy.

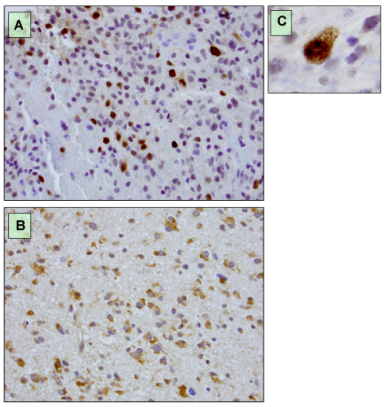

Figure 2: Immunohistochemical staining patterns of glioblastoma multiforme (GBM) formalin-fixed, paraffin embedded tissue specimens for survivin. (A) GBM showing predominant nuclear staining for survivin. (B) GBM with mostly cytoplasmic survivin expression and lack of nuclear staining. (C) Representative high magnification from a third GBM showing a cell with simultaneous cytoplasmic and nuclear survivin expression. [A, B 200x; C, 400x; anti-survivin clone 12C4 (Dako North America, Inc. Carpinteria, CA)].

Survivin Vaccines in Clinical Studies

A number of anti-tumor vaccine strategies have used cell-surface target molecules like HER2/neu, EGFR and EGFRvIII which are accessible to both cellular and antibody-mediated immune attack [52-56]. If correctly presented on the surface of tumor cells by MHC molecules, epitopes of intracellular proteins that are also recognizable by specific effector T cells can serve as targets for antitumor immune responses [25,26,57]. For example, studies in patients with malignant melanoma have demonstrated cytotoxic T lymphocytes (CTL) that recognize MHC-I-presented peptides derived from the intracellular protein tyrosinase [58]. Tyrosinase and gp100 are proteins that can serve as antigens that are recognized by CTL in melanoma patients [59-61]. Peptide epitopes from tumor-associated antigens (TAA), including survivin, can be recognized by cytotoxic T lymphocytes (CTL) in the context of MHC molecules [25,26,62]. Monitoring of T cell reactivity against survivin-derived peptides in a melanoma patient in remission following IL-2 based immunotherapy identified a persistence of functional CTL capable of recognizing surviving [63]. Other auto-reactive CTL responses to survivin have been observed in cancer patients as well [64-66]. Similarly, circulating anti-survivin antibodies have been detected in patients with colon and lung cancer [59-62]. These observations document the natural immunogenicity of survivin and underscore its potential utility as a target for cancer immunotherapy.

A number of survivin-targeting immunotherapeutic strategies have been developed to date. Dendritic cell (DC)-based vaccines are attractive due to the tremendous antigen presentation potential of DC. Dendritic cell vaccines pulsed with apoptotic bodies of cells that over-expressed survivin (as well as Her2, CEA, WT1 and MAGE2) have been studied in non-small cell lung cancer (NSCLC) [67]. This study showed positive immune responses in 10 of 14 patients, along with anecdotal clinical responses [67]. DC loaded with both survivin and

telomerase peptides have been tested in renal carcinoma where 13 of 27 patients experienced disease stabilization for 8 weeks along with 1 patient who had stable disease for 6 months [68,69]. In another study, DC pulsed with survivin and MAGE3 mRNA produced vaccine-specific CD3+ T cell production in multiple myeloma patients [70]. While detection of survivin-specific T cells in DC vaccine studies are encouraging, it is difficult to dissect the contribution of individual antigens in these reports since most have either included other target antigens along with a survivin CTL epitope (i.e. gp100, Muc1, telomerase and MAGE), or have simply used pulsed crude tumor lysate from survivin-expressing cells.

Several survivin peptide vaccines are also currently under development. In one early study, a patient with pancreatic cancer was vaccinated with a single survivin peptide and experienced a complete remission [71]. An HLA-A*24-restricted survivin-2B splice variant vaccine showed safety and produced immune responses in patients with advanced colorectal cancer [72]. Subsequent studies showed this peptide to be effective at stimulating CTL responses in patients with advanced breast cancer, oral and urothelial cancers [73-76]. Most recently, this peptide vaccine has shown promise in metastatic urothelial cancer where 30 patients had significantly better overall survival compared to controls [77]. This particular vaccine utilizes a very specific epitope that is not present in all survivin forms.

Other survivin peptide vaccines have incorporated combinations of HLA class I restricted survivin peptides. A phase II study of one such peptide combination showed prolonged overall survival in metastatic melanoma patients (median survival of 19.6 vs. 8.6 months) [78]. This anti-survivin vaccine peptide mixture (EMD640744) consists of five CTL epitope peptides, each with highly specific HLA class I restrictions [79]. A recent phase I study of EMD640744 in advanced solid tumors showed CD8+ T cell responses in 61% of patients and stable disease in 28% of treated patients [79]. A liposome-based adjuvant formulation of survivin peptide mixture known as DPX-Survivac has also induced survivin-specific CD8+ T cell immune responses in a phase I ovarian cancer study [80]. Further study of that agent is currently ongoing.

While CD8+ CTL responses are powerful anti-tumor targeting agents, CTL responses alone have not led to consistent clinical responses. A number of studies have highlighted the value of CD4+ T cells and antibody-based responses in enhancing anti-survivin immunotherapeutic efficacy [25,26,57,76,81]. Once CD4+ cells have been activated, they proliferate and produce cytokines (e.g. IFN-γ, IL-2, and IL-4) that enhance CTL immune responses [82-84]. In addition to simply recruiting CD4+ T cells via a generic helper peptide, the presence of MHC class II-restricted CD4+ T cells that are specific for tumor-associated antigens has been recognized to be an important element for providing essential helper factors in eliciting and sustaining cytotoxic CD8+ responses against tumors [81,82,85-88]. Therefore, a vaccine strategy that combines CTL and CD4+ antigen-specific support provides an additional avenue to improve survivin-targeted, vaccination approaches.

Pre-existing anti-survivin immune responses in cancer patients do not efficiently eliminate tumor cells in part due to weak potency of such responses which may be related to immunological tolerance. One mechanism that could be exploited to break tolerance to the wild-type survivin antigen is through molecular mimicry. A molecular mimic has the ability to activate cells not deleted during central immunological development. This may include T cells that retain the potential to cross-react with the wild-type tumor antigens [89]. T cell clones with the capacity to be activated by self-proteins are frequently preserved following negative selection of higher affinity, self-recognizing clones in the thymus [89]. Such potentially self-reactive cells remain tolerized under normal conditions [90]. Altered peptide ligands (mimics) can provide a way to break tolerance to the natural self-epitope [91,92]. Altered peptide ligands generated by substituting amino acids within a peptide epitope can markedly alter immune responses. This strategy may be used to increase the affinity of the peptide for MHC-I via alterations in the binding anchor residues [93,94]. While changes introduced can improve MHC class I binding, the subsequently engaging T cell does not always counter with an enhanced response and may lead to induction of TCR antagonism or T cell anergy [95-99]. The anti-survivin vaccine (SurVaxM) contains a large synthetic peptide with amino acid substitution designed to enhance MHC class I binding [25,57]. As a result the core epitope of SurVaxM binds HLA-A*02 molecules to a much greater degree than the wild-type survivin peptide leading to a more potent immune response than the wild-type survivin peptide in humans [25] (Figure 3).

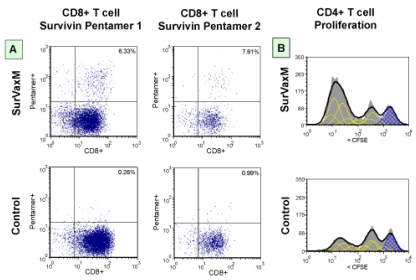

Figure 3: A) Flow cytometric analysis of pentamer binding (HLA-A*0201) to human survivin-specific CD8+ T cells stimulated ex vivo with SurVaxM. Specific reactivity of CD8+ T cells to two different survivin epitopes but not control peptide are shown (upper right quadrants are CD8+/Pentamer+). B) Flow cytometric measurement of CD4+ proliferation via CFSE dye mitotic distribution in response to ex vivo stimulation with SurVaxM. As CD4+ cells proliferate, CFSE intensity decreases as dye is re-distributed among daughter cells. Stimulation was without added peptide (Control) or with SurVaxM peptide. Grey, raw data; black line, computer curve fit; blue, undivided cells; yellow line, multiple proliferative generations. Data acquisition using BD LSRFortessa and analysis using FCS express v4. [anti-survivin custom pentamer (ProImmune, Oxford, UK) and CFSE (Invitrogen-Molecular Probes, Eugene, OR)].

While designed for HLA-A*02 binding, the entire SurVaxM peptide contains multiple HLA-A*02 epitopes as well as antigen-binding motifs for HLA-A*03; HLA-A*11, A24, A26, A68, B13, B14, B15, B35, B39 and B44, collectively representing a large patient population in which the peptide should be immunogenic [25,57]. An amino acid substitution in SurVaxM enables this mimic to be recognized as a non-self-protein, thus eliciting a strong immune response [25]. SurVaxM stimulates a group of survivin-specific CD8+ T cells and acts as a MHC class II ligand providing CD4+ T cell stimulation [25,26,57,100]. By activating multiple CD8+ CTL responses and CD4+ helper support (Figure 3), SurVaxM has a significant theoretical advantage as an active specific immunogen compared with survivin vaccines using a single class I-restricted peptide, or ones that incorporate generic helper

peptides, which produce non-specific helper support [25,26]. The peptide contained in SurVaxM is also located in a region common to most survivin splice variants which could allow it to simultaneously target several survivin variants. Currently SurVaxM is in Phase I clinical trials designed to study its safety, tolerability and immunological effects in patients with survivin-positive recurrent malignant gliomas and multiple myeloma [57].

Conclusion

Immunotherapy targeting survivin is still at an early stage of development; however, several agents are rapidly moving through phase I and phase II clinical trials. Recent studies demonstrate that the toxicity profile of this mode of vaccine therapy is good and that significant immune responses can be generated with some clinical responses apparent as well. Early indicators point to a strong rationale for continued study.

Disclosure

Financial & competing interests disclosure: The trial is registered with and was approved by the US FDA and by the local IRB at Roswell Park Cancer Institute (Study I-171010) in Buffalo, NY, USA. MJC and RAF are co-founders of MimiVax, LLC, which has a financial interest in SurVaxM. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

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