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# *CCR* 20th Anniversary Commentary: Stayin' Alive—Anti-apoptotic Proteins and Breast Cancer

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## Abstract

The control of cell death involves a complex interaction of multiple proteins. In a study published in the January 1, 2000, issue of *Clinical Cancer Research*, Tanaka and colleagues demonstrated that one of the pro-apoptotic proteins, *survivin*, was frequently expressed in breast cancer. In the subsequent years, effectors of apoptosis have translated into important prognostic indicators and potential therapeutic targets.

For many years, the regulation of cell growth has been at the guiding principle for treatment with cancer chemotherapy. Certainly, the first attempts at controlling cancer growth were via targeting cell cycle progression with drugs designed to interfere with nucleotide synthesis, alkylate DNA, inhibit enzymes involved in DNA replication, and affect tubular function. Strategies to inhibit estrogen receptor alpha (ERα), a key regulator of breast cancer cell proliferation, were also pursued. Treatment of metastatic breast cancer with these modalities has improved outcomes. The use of systemic therapy in operable breast cancer via the adjuvant administration of chemotherapy, hormonal therapy, or both has resulted in a steady reduction of breast cancer mortality for over two decades.

Clinical use of chemotherapy preceded a mechanistic knowledge of how cytotoxic drugs caused cell death. While the majority of effective agents in breast cancer were developed to inhibit cell cycle progression, it also became clear induction of apoptosis was critically important for chemotherapy-induced cell death. Apoptosis, described in the 70's, was seen as a mechanism used by organisms to lose cells in a programmed way, essentially a counterbalance for mitosis. Very early in the description of the process, the implications for disruptions in this pathway for cancer were evident (1).

Multiple triggers initiate apoptosis. Central to many of the triggers is the induction of caspases, a family of cysteine proteases, which are activated post-translationally. Cleavages of the pro-enzymatic forms are frequently used as markers for induction of apoptosis. Inhibitors of Apoptosis (IAPs) also exist and can function to inhibit caspase activation thereby preventing apoptosis. Survivin is an IAP family member and in conjunction with

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other proteins, most notably XIAP, functions to inhibit caspase activity and has an important role in disrupting apoptosis (2). While survivin has potentially many additional functions, the inhibition of apoptosis is directly relevant to cancer biology and therapy (3).

Tanaka and colleagues demonstrated survivin expression, as measured by immunohistochemistry, was associated with poor outcome in primary breast cancers (4). High levels of survivin expression reduced the apoptotic index and was also positively associated with high levels of bcl-2, another anti-apoptotic protein. Thus, just as high proliferative rate was linked to breast cancer outcomes (5), we now had information that low apoptotic rates, as potentially regulated by anti-apoptotic proteins, could also play a role in breast cancer.

Information provided by Tanaka and colleagues has been used in several ways to impact breast cancer therapy. As with any prognostic factor, these data need to be used to develop better strategies for our patients. Perhaps one of the first uses, incorporating apoptotic proteins into a clinical decision making tool, came from the 21-gene assay (commercialized as OncotypeDx®) which includes both survivin and bcl-2 in the assay (6). This assay, based on RT-PCR expression derived from paraffin blocks, categorizes ERα into low, intermediate, and high risk tumors. While the quantitative contribution of each gene in the assay is not explicitly given in the clinical results, survivin is one of the genes determining the high-risk designation.

Additional multigene assays have been developed to evaluate breast cancer prognosis. The 70-gene assay (MammaPrint®) does not directly measure survivin, but two other genes associated with anti-apoptosis (BBC3, EGLN1) are included in the assay. The PAM50 classifier (Prosigna®) also includes bcl-2 in its assay of 50 genes. Thus, demonstration how survivin and anti-apoptotic genes have a role in breast cancer prognosis has resulted in the inclusion of these genes in prediction classifiers used in clinical practice. While the contribution of each individual gene cannot be clearly determined due to the way the assays are reported to the clinician, it is clear the work of Tanaka and colleagues has direct clinical utility.

An important reason to identify prognostic factors in breast cancer is with a goal of developing a more detailed molecular understanding of the factor. For example, HER2 gene amplification was one of the first genetic markers associated with poor prognosis. Subsequent research focused on understanding the function of this oncogene has resulted in landmark clinical advances in the targeting of this molecule. Certainly, the clinical benefits of trastuzumab to “neutralize” the poor prognosis of women whose tumors express HER2 has been one of the most important translational outcomes for breast cancer in the past 25 years (7) and has provided future potential avenues for research.

This same improved clinical outcome has not yet been achieved for targeting of survivin. Several strategies, including anti-sense strategies (gataparsen - LY2181308) and small molecule inhibitors (sepantronium bromide) have been tested in clinical trials with disappointing results (8–11). Most of these trials were utilized concurrent chemotherapy, the standard of care for many advanced malignancies. While this potentially should work, there

are many overlapping pathways that might compensate for survivin suppression. Importantly, most of the trials did not include an assay to measure survivin expression in the tumor. The development of predictive biomarkers was critical to the development of anti-HER2 strategies. Similar biomarkers might be necessary for targeting of survivin.

Additionally, targeting a molecule as heavily integrated into a coordinated signaling pathway with potential redundant pathways might require co-targeting with other key members of the pathway. It seems likely that multiple IAPs and other anti-apoptotic proteins will need to be targeted in conjunction with survivin targeting. Ongoing efforts to target bcl-2 and XIAP will help illuminate the benefit of disrupting these pro-survival signals. Thus, initial disappointment in targeting survivin might be due to a need to develop co-targeting strategies.

Thus, Tanaka and colleagues showed an anti-apoptotic protein, survivin, has a prognostic role in breast cancer. This finding has been incorporated into several, current standard-of-care, multi-gene tools to define breast cancer prognosis. Mechanistically, cells shifted to survive an apoptotic insult should be more resistant to current treatments. It follows that additional strategies to inhibit these anti-apoptotic strategies should improve outcomes. However, this has not yet been shown with the current approaches. Perhaps a more comprehensive evaluation and co-targeting of these pathways will result in the promising early results demonstrated in this paper.

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