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Survivin: apoptosis inhibitor and its regulation by Hsp90

Tumor cells exhibit extraordinary adaptation to environmental stresses, which involves increased resistance to apoptosis and constitutive upregulation of cellular stress response. Notably, the former requires inhibitor of apoptosis (IAP) genes and the latter requires protein folding control by heat-shock proteins (Hsps) among others.

Survivin, at 16.5 kDa, is the smallest mammalian member of IAP gene family. Structurally, it contains a single Baculovirus IAP Repeat, that is, ~70-amino-acid zinc-finger fold that is the hallmark of all IAPs. A single copy of the survivin gene is located on chromosome 17q25 in humans, which gives rise to three alternatively spliced survivin transcripts. Survivin may play a more selective role than other IAPs in antagonizing mitochondrial-dependent apoptosis. A sharp differential expression in cancer *vs* normal tissues is one of the most intriguing features of survivin, and is unlike any other IAPs. In addition, several retrospective studies have found that survivin was a reliable marker of aggressive and unfavorable disease progression in various malignancies, and was associated with abbreviated overall survival.

Hsps comprise evolutionary conserved ATPase-directed molecular chaperones. In particular, Hsp90 controls the balance between folding/maturation and proteasomal destruction of a restricted number of client proteins that are typically involved in signal transduction and cell proliferation. This pathway is exploited in cancer where Hsp90 is upregulated and may be linked to resistance to apoptosis.[1]

A newly published study by **Fortgno *et al*** was able to demonstrate Hsp90 association with survivin.[2] The full-length Hsp90 with its ATP-binding site bound recombinant survivin. The Lys-79-Lys-90 survivin peptide was the complementary Hsp90-binding site on survivin and is located in the conserved Baculovirus IAP repeat of survivin. The folding of survivin was required for Hsp90 binding. In addition, this study also found that the chaperone function of Hsp90 was required for survivin stability *in vivo* and loss of survivin after Hsp90 inhibition involved proteasomal-dependent destruction. Cytoprotection by the survivin–Hsp90 complex was centered on the mitochondrial pathway, in agreement with the role of survivin in regulating mitochondrial apoptosis and caspase-9 recruitment to the Apaf-1 apoptosome.

This study was able to identify survivin as a new client protein for Hsp90, linking the cellular stress response to a dual cell viability/mitotic checkpoint. Disruption of the survivin–Hsp90 interaction destabilizes survivin, initiates mitochondrial apoptosis, and suppresses cell proliferation. 'Molecular antagonists of the survivin–Hsp90 interaction may provide a rational approach to critically lower this anti-apoptotic threshold and promote targeted elimination of cancer cells', commented Dario C Alteri, senior investigator of this study.

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Is metastatic potential of breast cancer inherent or acquired?

Most patients with breast cancer die of metastatic disease rather than from the primary tumor. For years, researchers have tried to identify molecular markers or a molecular signature associated with metastatic potential. Their working hypothesis was based on the concept that metastasis resulted from selection of rare cancer cells with critical gene alterations within the primary tumor, and that the emergence of these molecular markers was the end result of genomic instability of tumor cells, environmental pressure, and proliferation or survival advantage of these mutations. *In vitro* and animal studies have found that alterations of some genes, including cathepsin D, nm23, E-selectin, maspin, PTEN, and matrix metalloproteinases (MMPs), were associated with high metastatic potential and were acquired late during tumorigenesis.

Recent discoveries made by two independent groups of investigators, however, have challenged the above concept.[1,2] **Weigelt *et al***[1] compared gene expression profile using cDNA microarray technique in eight paired primary breast carcinomas and their metastases. They found that there was a striking genetic similarity between the primary and the metastatic carcinoma, using unsupervised hierarchical clustering, multidimensional scaling, and permutation test. The similarity between the paired primary and metastatic carcinoma was greater than that between primary tumors from different individuals. Therefore, there were no molecular markers or a molecular signature to distinguish primary

tumors from their metastases. **Ramaswamy *et al***[2] using a different approach and research design also came up with a similar conclusion. They examined gene expression profiles of 279 solid carcinomas including breast cancers by oligonucleotide microarrays, and found a 17-gene cluster of metastasis molecular signature. However, this molecular signature was also present in a subset of primary tumors. Results from these studies suggested that metastatic potential is inherent rather than acquired by selective cells within a heterogeneous primary tumor.

This new concept not only provides a different view on the understanding of how tumors metastasize but also leads us to rethink of how to manage patients with breast carcinoma, how to design new drugs, and how to predict therapeutic response and prognosis.

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