

Commentary

Synergy of Pancreatistatin and Tamoxifen in inducing apoptosis in breast cancer cells

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The development of chemotherapeutics for cancer has as its holy-grail, targeted reagents and better still, synergistic combinations of such selective reagents. Breast cancer has at least two widely used targeted therapies: the anti-epidermal growth factor receptor monoclonal antibody Herceptin for HER-2 positive cancers and the anti-estrogen tamoxifen for estrogen receptor positive tumors.

In a series of publications over the past 3 years Dr. Pandey's group at the Univ of Windsor in collaboration with Dr McNulty at McMaster have shown that pancreatistatin, an alkaloid derived from the Hawaiian spider lily (fam. amaryllidaceae) induces apoptosis selectively in several cancer cell lines while sparing cognate normal cell lines by selectively targeting the mitochondria (1-5).

In this issue of *Cancer Biology & Therapy*, Siedalowski et al. have demonstrated the synergy between tamoxifen and pancreatistatin, on both estrogen receptor positive and negative human breast cancer cell lines in vitro. The authors claim that pancreatistatin disrupts the mitochondrial membrane potential leading to apoptosis specifically in breast cancer cells with minimal toxicity to normal mammary cell lines. Cancer cells treated with pancreatistatin and tamoxifen experienced destabilization of the mitochondrial membrane, leading to increased production of reactive oxygen species. They propose that low doses of tamoxifen (5 μ M) may target the mitochondria, binding with flavinmononucleotide at complex I, but not cause sufficient damage to induce apoptosis (10, 12, 9). It has also been reported that tamoxifen increases inter-membrane Ca²⁺ concentrations and stimulated NO₂ synthase activity leading to hampered mitochondrial respiration and release of cytochrome c thereby implicating nitric oxide synthase activity as critical for mitochondrial destabilization and apoptosis (9, 11).

There is considerable evidence suggesting that the mitochondria of cancer cells are different in structure and/or function as compared to their normal counterparts (6). Renewed interest in the mitochondria as a target for innovative cancer chemotherapies has increased over the last few years. Recent studies indicate that changes in the protein and lipid composition of the mitochondrial membrane make cancerous cell mitochondria more vulnerable to selective chemotherapeutics like Pancreatistatin (1, 6). One current chemotherapeutic strategy utilizes lipophilic cations that accumulate selectively in carcinoma cells in response to increased mitochondrial membrane potential. Several of these compounds have exhibited at least some degree of efficacy in killing cancerous cells in vitro and in vivo 13-20. The many distinct differences in mitochondrial structure and function between normal cells and cancer cells offer the potential for the clinical use of mitochondria as targets for novel and site-specific anti-cancer agents 21-22.

The combination of pancreatistatin and tamoxifen effectively bypasses the p53-induced mechanism of apoptosis, thus making this treatment effective for a large number of tumors containing wild type and mutated p53. Estrogen receptor negative breast cancer is currently an "orphan disease" without any targeted therapy. The fact that this combination works independent of estrogen receptor expression is particularly unique and exciting. These results have broader implications for cancer drug development, and open the door to other possible modulators of mitochondria as potential selective treatments for cancer.

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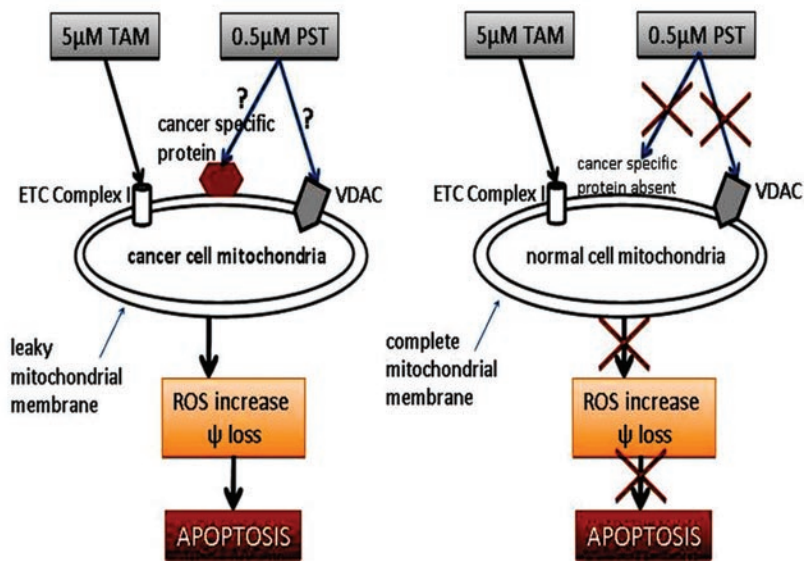


Figure 1. Possible biochemical mechanism of synergistic action of Pancreatistatin (PST) and Tamoxifen (TAM). Cancer cell mitochondria may be more sensitive to targeted therapy; question marks indicate that the exact target of PST is yet to be identified. Tamoxifen has been shown to bind to complex I (9, 10) and may sensitize cancer cells to low dose PST treatment.

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