Is Tamoxifen the Rosetta Stone for Breast Cancer?

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During the closing stages of the 18th century, a young French general named Napoleon Bonaparte led an expedition from France to Egypt. The goals were to: 1) establish a base for an advance over land to attack British interests in India, and 2) collect scientific information and artifacts from the ancient land of Egypt. Unfortunately, the military campaign turned into a strategic disaster when Admiral Nelson sank Napoleon’s transport fleet in the Battle of the Nile. History was to record, however, that the Egyptian venture was not a complete failure; the scientific expedition uncovered an artifact that would become the conduit to relive the story of a lost civilization.

In the ruins surrounding the French soldiers were strange drawings known as hieroglyphs. No one had any idea what the designs meant until chance intervened. French troops who were tasked to strengthen the defenses of an abandoned fort near Rosetta uncovered a large stone slab inscribed with a text in three distinct languages: Greek, which scholars could understand, an unknown script (demotic), and hieroglyphs. The scientists in the party recognized the potential importance of the artifact in deciphering hieroglyphs and, thus, carefully preserved it for future study. For years, no one could translate the artifact, now known as the Rosetta Stone; however, a young Frenchman named Jean François Champollion did eventually succeed, and the story of a powerful empire in Egypt came alive.

Tamoxifen was discovered by the late Dr. Arthur L. Walpole, who led the antifertility program at ICI Pharmaceuticals Division (U.K.) during the early 1960s (1). Although the initial goal of developing a contraceptive was a strategic disaster and, in fact, failed, the academic community worked with staff at ICI Pharmaceuticals Division throughout the 1970s to advance a secondary goal: to develop tamoxifen as a novel targeted breast cancer treatment (2,3). For the past 20 years, tamoxifen has been the endocrine treatment of choice for all stages of estrogen receptor (ER)-positive breast cancer (4). An analysis of randomized clinical trials (5) suggested that hundreds of thousands of women are alive today because of the widespread use of adjuvant tamoxifen therapy. However, it is also clear that tamoxifen is not effective in all ER-positive breast cancers, and the question to be asked is, why? The fact that the pharmacology of tamoxifen has been rigorously investigated means that tamoxifen’s action as an antiestrogen is subverted by the molecular configuration of the cell, or the cell has adaptive mechanisms that rapidly convert tamoxifen from an antiestrogen to an estrogen. Indeed, knowledge of the triumvirate of ER, cell-surface signaling, and coactivators (Fig. 1) has been used previously to understand the actions of selective estrogen receptor modulators (SERMs) (e.g., tamoxifen and raloxifene). Simply stated, SERMs are antiestrogens at some target tissue sites such as the breast but estrogens at others such as bone. Shang and Brown (8) have recently shown that the concentration of another ER coactivator SRC-1, which is related to SRC-3, but not SRC-3 itself, can enhance some ER-mediated genes in endometrial cancer cells where tamoxifen has estrogen-like effects. Levels of SRC-1 were transiently increased or decreased in cells to modulate gene activation by tamoxifen. However, this process did not work for wild-type breast cancer cells. Unfortunately, Shang and Brown (8) did not include the critical role of active cell-surface signaling in their experimental model, despite the fact that Brown’s group has already shown that cell-surface signaling can enhance SRC-3 phosphorylation and ER activation (9).

In this issue of the Journal, Osborne et al. (6) describe an interaction between breast tumors that are HER-2/neu-positive and high levels of the ER coactivator SRC-3 (also called AIB1) that correlate with poor outcome when adjuvant tamoxifen is used in ER-positive disease. Although the proportion of women affected by poor outcome was only 10% of the Osborne et al. study population, the authors stress that prospective studies and further analysis of existing clinical trials are required to validate these important findings. A good place to start this analysis would be to look at the Arimidex and Tamoxifen Alone or in Combination (ATAC) adjuvant trial (7), which has already noted an early increase in disease-free survival (DFS) of breast cancer patients treated with the aromatase inhibitor anastrozole when compared with that of patients treated with tamoxifen. It is important to find out whether tumors with high SRC-3 and HER-2/neu expression that do not respond to tamoxifen might respond to an aromatase inhibitor. Then, as the authors suggest, a test would be in place to allow physicians to continue to prescribe tamoxifen for the majority of breast cancer patients.

Although it is a reasonable goal to develop a predictive test for tamoxifen resistance, it may be more useful to examine the extensive literature on the molecular pharmacology of tamoxifen and to use that information to decipher the individual associations in clinical studies. In this way, the predictable changes that tamoxifen can induce in the breast cancer cell could provide a rational road map for patient care.

Although Osborne et al. (6) focus on two apparently independent variables, HER-2/neu expression and the ER coactivator SRC-3, it is, in fact, the amount of ER that links the previous two factors together, and all three of these factors must be used to decipher the consequences of antiestrogen action. This triumvirate (i.e., group of three controlling variables) appears to regulate the intrinsic or rapidly acquired resistance observed with tamoxifen therapy (6). In other words, tamoxifen’s action as an antiestrogen is subverted by the molecular configuration of the cell, or the cell has adaptive mechanisms that rapidly convert tamoxifen from an antiestrogen to an estrogen. Indeed, knowledge of the triumvirate of ER, cell-surface signaling, and coactivators (Fig. 1) has been used previously to understand the actions of selective estrogen receptor modulators (SERMs) (e.g., tamoxifen and raloxifene). Simply stated, SERMs are antiestrogens at some target tissue sites such as the breast but estrogens at others such as bone. Shang and Brown (8) have recently shown that the concentration of another ER coactivator SRC-1, which is related to SRC-3, but not SRC-3 itself, can enhance some ER-mediated genes in endometrial cancer cells where tamoxifen has estrogen-like effects. Levels of SRC-1 were transiently increased or decreased in cells to modulate gene activation by tamoxifen. However, this process did not work for wild-type breast cancer cells. Unfortunately, Shang and Brown (8) did not include the critical role of active cell-surface signaling in their experimental model, despite the fact that Brown’s group has already shown that cell-surface signaling can enhance SRC-3 phosphorylation and ER activation (9).
Fig. 1. Integrated mechanism for the target site-specific action of selective estrogen receptor modulators (SERMs) in breast and uterine cancer. Two extremes of antiestrogenic or full estrogenic actions are shown. Estrogen-like actions could occur in cells expressing an excess of coactivators (CoAs) and/or a decrease in corepressors (CoRs). The charged surface of a tamoxifen–estrogen receptor (ER) complex at AF2b prevents CoR binding. The estrogenic action would be amplified by surface signaling with dimers of epidermal growth factor receptor (EGFR) and HER-2/neu activating tyrosine kinases (tk). The phosphorylation cascade can activate either AF-1 on ER-alpha (ER\(^\alpha\)) or HER-2/neu (HER\(^\beta\)). The former, which is the activation of the tamoxifen–ER complex, either directly (through phosphorylation cascades) or indirectly (through phosphorylation of the coactivator), is an elegant solution to the problem of tamoxifen-resistant disease. Nevertheless, the question must be asked whether the physician can already subvert the power of the triumvirate by the judicious use of new approaches to endocrine therapy in select patients? In laboratory models of acquired drug resistance to tamoxifen, the antiestrogen fulvestrant (ICI 182,780) controls tumor growth by destroying the ER (18, 19). Fulvestrant is effective in approximately one in five patients who are resistant to tamoxifen (20, 21). Furthermore, the improved DFS observed with anastrozole (7) most likely also results from the disruption of the triumvirate (Fig. 1). The inhibition of estrogen synthesis by an aromatase inhibitor will prevent the formation of an ER complex at the target gene sites of tumor cell survival. It is reasonable to say that, for the clinician, the new generation of endocrine agents will enhance therapeutic benefits without further detailed knowledge of individual mechanisms. The challenge will be, therefore, to address the treatment of antihormonal therapy-resistant ER-positive patients. It is possible, however, that the ER will again be the target of the fall of the triumvirate (22).

In conclusion, Dr. Bernard Fisher recently presented a lecture entitled “Tamoxifen: the Rosetta Stone or Hope Diamond?” There is no doubt that the merits of tamoxifen have been vigorously contested and debated (23–25). Nevertheless, the combined advantages of being a pioneering life-saving medicine (5, 26) and an agent to decipher the molecular perturbations of the breast cancer cell make tamoxifen, on balance, the Rosetta Stone.

REFERENCES

Tamoxifen for early breast cancer: an overview of the randomised trials.


