Tamoxifen-induced Enhancement of Calcium Signaling in Glioma and MCF-7 Breast Cancer Cells

Wei Zhang, William T. Couldwell, Hua Song, Takahiro Takano, Jane H. C. Lin, and Maiken Nedergaard

Abstract

The antiestrogen tamoxifen is commonly used to treat breast cancer, but it also has therapeutic activity in several other types of cancer. Many of these tumors, including malignant gliomas, are estrogen receptor negative. Nonetheless, high concentrations of tamoxifen can directly reduce cell proliferation in some of these tumors and induce apoptosis. In this study, the role of tamoxifen in calcium signaling and calcium-induced cell death was studied in both malignant glioma cell lines and MCF-7 breast cancer cells. Tamoxifen potently increased the spatial expansion of calcium waves by 30–150% while significantly enhancing and prolonging agonist-induced calcium elevations. Furthermore, tamoxifen pretreatment accelerated calcium ionophore-induced death by more than 20 min, suggesting that tamoxifen lowered cellular resistance to calcium loads. In contrast to its potentiating of calcium signaling in tumors, tamoxifen had no significant effect on calcium signaling in cultures of primary astrocytes from either human or rat brain. This study demonstrates the existence of calcium signaling in breast cancer and glioma cells and identifies tamoxifen as a potential modulator of tumor-associated calcium signaling.

Introduction

Waves of elevated cytosolic calcium that travel from cell to cell constitute a newly discovered form of long-range signaling (1). Calcium waves may serve to synchronize physiological response to external stimulation but have also been implicated in propagation or amplification of injury. In stroke, secondary damage correlates directly with the extent of propagating calcium waves, and in cell culture models, apoptosis can spread to include otherwise resistant cells by elevations in cytosolic calcium levels (2). A related mechanism is bystander death, in which transfer of ganciclovir from thymidine kinase-expressing cells eradicates their kinase-deficient neighboring cells (3).

This study was prompted by our observation that the widely used antitumor agent tamoxifen greatly enhanced long-distance calcium signaling in both breast cancer cells and several primary glioma cell lines. Tamoxifen not only increased the radius of calcium wave propagation induced by local stimulation but also increased the amplitude of agonist-induced calcium elevations while retarding the normalization of cytosolic calcium.

We speculated that the antitumor action of tamoxifen might be linked to deregulation of local calcium signaling. The spontaneous rate of apoptosis is high among anaplastic cells, and necrotic tumor centers are common (4). In the presence of tamoxifen, local apoptotic events might spread to include neighboring tissue. In support of this mechanism, we demonstrate that ionophore-induced increases in cytosolic calcium resulted in the widespread death of tamoxifen-treated glioma cells, but not of untreated glioma cells. In contrast to the potent action of tamoxifen on both glioma and breast cancer cells, tamoxifen had no significant effects on astrocytic calcium signaling.

Materials and Methods

Primary Cultures. Rat astrocytic cultures were derived from newborn (1 day postnatal) brain and prepared using a standard primary culture procedure in our laboratory as described previously (5). Experiments were performed after 10–14 days in vitro.

All human brain tissue was from surgery performed at the Department of Neurosurgery, Westchester Medical Center with the approval of the institutional review board. Adult human temporal lobe was collected from anterior temporal lobectomy performed as treatment for refractory epilepsy. The protocols for preparation of human astrocytic and glioma cell cultures have been described previously (6). Cultures were discharged after two passages.

Cell Lines, Transfection, and Selection. Rat C6 glioma cells and MCF-7 breast cancer cells were obtained from American Type Culture Collection (Manassas, VA), and C6 cells were also transfected with Cx43. The cDNAs for Cx43 were ligated into pcDNA1 expression vectors containing the genes for Geneticin resistance (kindly provided by K. Willecke, Bonn University, Bonn, Germany), and stable transfectants were selected with 2 mg/ml Geneticin. Expression of Cx43 was assayed by immunolabeling and functional dye transfer. Native C6 cells express little Cx43 immunoreactivity, and the control transfectants, like their parental C6 cells, express no detectable Cx43.

Cell Preparation and Tamoxifen Treatment. Glioma cells, MCF-7 breast cancer cells, and astrocytes from both human and rat were seeded into 24-well cell culture plates (Falcon) containing 12-mm coverslips at densities ranging from 0.5–1.0 × 10^5 cells/well. Cell cultures were then incubated at 37°C for 24–48 h and treated with tamoxifen (0.1–10 μM) for 2, 24, or 48 h. In all experiments, control sister cultures were treated with an equivalent volume of the vehicle ethanol (maximum, 0.1%).

Intercellular Ca^{2+} Signaling. Cytosolic Ca^{2+} levels were quantified using Image-1 software (Universal Imaging) and a SIT camera (Dage, Inc.) as described previously (2). Intercellular calcium signaling was analyzed as described previously (6). Confluent cultures were loaded for 1 h with 5 μM Fluo-3 acetoxymethyloxyster (Bio-Rad, Hercules, CA). All experiments were performed at room temperature. To initiate a Ca^{2+} wave, a cell in the center of the viewing field was mechanically stimulated by a patch pipette (tip diameter, <1 μm) mounted on a micromanipulator (MMP-220; Narishige). Excitation was provided by the 488 nm line of a krypton-argon laser using a Bio-Rad confocal microscope. The radius of calcium waves was measured as the maximal distance traveled by the calcium wave from the point of initiation. The relative increase in cytosolic calcium was calculated as ΔF/Δt, where ΔF = F1 (the treatment-associated Fluo-3 emission) ~ F0 (the unstimulated baseline Fluo-3 emission). Occurrence of calcium waves was defined as a 50% increase
in ΔF/F0 that propagated for a minimum of 50 μm in at least one direction. Background counts were subtracted from all measurements.

**FRAP and Immunocytochemistry.** Gap junctional function was assessed by the FRAP technique as described previously (2). Immunocytochemical staining against Cx43 was performed as described previously (5, 6). A polyclonal antibody directed against the cytoplasmic COOH-terminal of Cx43 was kindly provided by Dr. Bruce Nicholson (SUNY Buffalo, NY). Immunofluorescence was visualized by confocal microscopy and counterstained to visualize nuclei.

**ATP Quantification.** ATP determinations were carried out using a bioluminescent ATP assay kit (Sigma) and a Chrono-Log luminometer. Cells were grown in 24-well tissue culture plates. Each well was half-washed six times with DMEM:Ham’s F-12 and incubated for 20 min in 400 μl of DMEM. Samples of the supernatant were collected immediately before and 10 min after exposure to 100 μM UTP. Stimulated ATP release was calculated as the difference between the two samples and normalized as a function of cell number. A maximum vehicle of 0.1% ethanol was added to standards. A minimum of three wells in three independent experiment were evaluated (n = 9). Cell number was determined after dissociation in each experiment.

**Cell Viability.** Cell viability was evaluated using the alamar blue assay. Cells were grown in 24-well plates for 1 day. The cultures were exposed to the calcium ionophore lasalocid (40 μM) as described previously (5). Two h before the ionophore exposure, the cultures were first treated with 10 μM tamoxifen or with 0.1% ethanol as a negative control. Twenty h later, alamar blue (Biosource International, Camillo, CA) was added. All measurements were taken after a 4-h incubation period with the dye. Living cells metabolize alamar blue, resulting in a shift in maximal absorbance from 600 nm to 570 nm. Cell viability is represented as the difference in absorbance at the two wavelengths (ΔA\text{570 nm} − ΔA\text{600 nm}).

**Statistical Analysis.** ANOVA and Fisher’s post hoc tests were used to compare groups in all assays.

**Results**

**Tamoxifen Increases Both Resting Calcium Concentrations and Agonist-induced Calcium Increments.** As reported previously, the resting cytosolic calcium levels of C6 glioma cells were 80 ± 5 nM (mean ± SE; n = 39) in fura-2-loaded cultures (5). Tamoxifen exposure (10 μM tamoxifen) slowly increased calcium concentrations to 96 ± 5 nM (n = 58; P < 0.05) over a 2-h observation period. The purinergic receptor agonist ATP (100 μM) induced peak increases in cytosolic calcium of 412 ± 28 and 510 ± 19 nM in control and tamoxifen (2 h; 10 μM)-treated cultures (Fig. 1A), respectively (P < 0.01). Normalization of cytosolic calcium was also consistently delayed in tamoxifen-treated cultures compared with controls.

![Fig. 1. Tamoxifen-enhanced intercellular calcium signaling in malignant glioma cells.](#)

A. tamoxifen increased the amplitude of calcium elevation in response to ATP (100 μM) and slowed normalization of calcium. Cultures were pretreated with tamoxifen (2 h, 10 μM) and loaded with fura-2 am. Data are the mean ± SE of 38 (control vehicle-treated) and 58 (tamoxifen-treated) cells from of a total of 12 experiments. B, tamoxifen induced a dose-dependent increase in calcium wave radius in two human glioma cell lines. All cultures were pretreated for 2 h before analysis of calcium wave propagation with 0 (vehicle), 0.1, 1.0, or 10 μM tamoxifen. C and D, tamoxifen increased the radius of propagating calcium waves in C6 glioma cells. Four representative calcium waves were color coded (red, orange, yellow, and green) and superimposed to display the spatial expansion of calcium waves in control vehicle-treated cultures (C) and tamoxifen-exposed cultures (D; 2 h, 10 μM). Bar, 75 μm.
Long-distance Calcium Signaling Is Enhanced by Tamoxifen in C6 Gliomas and Several Primary Human Glioma Cell Lines. Local calcium signaling was analyzed in subconfluent cultures loaded with Fluo-3 and viewed by confocal microscopy. Single cells were stimulated by a patch pipette as described previously (5). C6 cells propagated relatively small calcium waves, with an average radius of $59 \pm 7 \mu m (n = 8)$, as reported previously (5). Tamoxifen ($10 \mu M$; 2 h) increased this radius to $148 \pm 12 \mu m (P < 0.01; n = 8$; Fig. 1C). Also, the relative elevation in cytosolic calcium ($\Delta F/F_0$) during calcium wave propagation increased to a greater degree in tamoxifen-treated cultures than in vehicle-treated controls (Table 1). The tamoxifen-induced enhancement of calcium signaling persisted at 24 h. Calcium waves in tamoxifen-treated cultures were 64% larger than those in matched control cultures at 24 h ($P < 0.001$).

In addition, we noted that human primary glioma cultures generated even larger calcium waves than C6 glioma cells. Typical wave propagation was averaged (100–170 $\mu m$) from the point of stimulation (Table 1). Nonetheless, human glioma cells also responded to tamoxifen, and the radius of wave propagation was further increased in a dose-dependent fashion (Fig. 1B).

Tamoxifen also Increases Calcium Signaling in the MCF-7 Human Breast Cancer Cell Line. Calcium signaling among breast cancer cells has not hitherto been explored. We found that the human breast cancer cell line MCF-7 propagated robust calcium waves, with an average radius of $221 \pm 24 \mu m$ (Fig. 2). Tamoxifen ($10 \mu M$; 2 h) increased this radius even further ($293 \pm 47 \mu m; P = 0.02$). Interestingly, calcium signaling in MCF-7 cells did not require cellular contact; in fact, the calcium waves traveled readily across cell-free areas (Fig. 2). Importantly, the purinergic receptor antagonists reactive blue (100 $\mu M$) and suramin (100 $\mu M$) both significantly reduced the mean radius of calcium waves by 52% and 24% respectively ($P < 0.001; n = 7$). Together, these observations strongly support the notion that an extracellular purine nucleotide, possibly ATP, mediates calcium signaling among breast cancer cells (5).

Tamoxifen Selectively Enhances Purinergic Signaling. Several studies have demonstrated previously that calcium signaling is mediated by both gap junction-mediated diffusion of intracellular messengers (Ca$^{2+}$ and/or inositol 1,4,5-triphosphate) and a pathway that includes release of ATP, with the activation of purine receptors on neighboring cells. These signaling mechanisms appear to coexist in most cell types studied thus far. Importantly, the two pathways can be regulated independently of each other. In this regard, several lines of evidence indicate that tamoxifen enhances calcium signaling by selectively amplifying purinergic signaling. First, tamoxifen-treated cultures (both breast cancer and C6 glioma cells) displayed stronger calcium responses when exposed to ATP (Fig. 1A), and they exhibited 3-fold increases in ATP release after stimulation (Fig. 2). Second, tamoxifen treatment increased calcium signaling despite the fact that

**Table 1** Effect of tamoxifen on intercellular calcium signaling in glioma cells and astrocytes

<table>
<thead>
<tr>
<th>Cell cultures</th>
<th>Calcium wave radius (µm)</th>
<th>Relative calcium increases ΔF/F0 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Rat</td>
<td>216.0 ± 17.0</td>
<td>191.0 ± 6.8</td>
</tr>
<tr>
<td>Astrocytes</td>
<td>152.6 ± 5.6</td>
<td>177.2 ± 5.8</td>
</tr>
<tr>
<td>C6 glioma (Cx43⁺)</td>
<td>59.2 ± 6.8</td>
<td>148.3 ± 12.3</td>
</tr>
<tr>
<td>C6 glioma (Cx43⁻)</td>
<td>173.3 ± 11.5</td>
<td>162.9 ± 11.6</td>
</tr>
<tr>
<td>Human</td>
<td>169.7 ± 11.5</td>
<td>206.0 ± 11.5</td>
</tr>
<tr>
<td>Astrocytes</td>
<td>173.2 ± 11.6</td>
<td>170.4 ± 16.2</td>
</tr>
<tr>
<td>GBM1</td>
<td>103.3 ± 9.8</td>
<td>172.3 ± 11.3</td>
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<tr>
<td>GBM2</td>
<td>146.2 ± 9.0</td>
<td>200.2 ± 10.3</td>
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<tr>
<td>GBM3</td>
<td>114.2 ± 9.0</td>
<td>170.4 ± 16.2</td>
</tr>
<tr>
<td>GBM4</td>
<td>114.2 ± 9.0</td>
<td>170.4 ± 16.2</td>
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</tbody>
</table>

*P < 0.01.

Fig. 2. Tamoxifen increased the radius of calcium waves in MCF-7 breast cancer cells. Culture was loaded with Fluo-3 and imaged by confocal microscopy. A sequence of images was collected 1, 8, and 16 s after focal mechanical stimulation. A, untreated MCF-7 breast cancer cells propagated larger calcium waves than C6 glioma cells (Fig. 1). B, preincubation with tamoxifen (10 $\mu M$) for 2 h increased the spatial expansion of calcium wave propagation in a sister culture. Note that the calcium wave "jumps" across cell-free areas, indicating that a releasable extracellular messenger mediates cell-cell signaling. Confocal laser gain and aperture settings were identical, and color scale indicates relative changes in Fluo-3 signal ($\Delta F/F_0$). Bar, 75 $\mu m$. C, tamoxifen significantly increased purinergic-stimulated ATP release from both MCF-7 breast cancer cells and C6 glioma cells, but not from cultured astrocytes ($P = 0.23$). Y axis, ATP (pmol/10⁶ cells). **, P < 0.001.
both gap junction expression and function were not significantly altered (Fig. 3). For these studies, we used C6 glioma cells stably transfected with Cx43 (C6-Cx43 cells; Ref. 2). As shown in Fig. 3, tamoxifen did not increase Cx43 immunoreactivity. Functional gap junction coupling was evaluated by using the FRAP technique. Gap junction coupling did not differ significantly between tamoxifen- and control-treated sister cultures (Fig. 3). Collectively, these results indicate that the tamoxifen-induced enhancement of calcium signaling is mediated by increased purinergic signaling.

**Tamoxifen Lowers the Threshold for Calcium-induced Glioma Cell Death.** Calcium elevation comprises a final common pathway leading to cell death. We therefore asked whether the tamoxifen-induced enhancement of calcium signaling might be associated with an increased sensitivity to otherwise sublethal calcium increases. To test this postulate, C6 cells were exposed for increasing periods of time to the calcium ionophore lasalocid (40 μM). The ionophore induced a robust increased in calcium and killed C6 glioma cells in a time-dependent fashion. In addition, tamoxifen lowered the threshold for lasalocid-induced cell death, as illustrated in Fig. 4. Hoechst staining of cultures exposed to lasalocid 24 h earlier revealed that 60–70% of the cells died in a process that shared many features with apoptotic cell death: the cells became pyknotic and contained small, fragmented, apoptotic nuclei. The remaining cells were left as “cellular ghosts” without nuclei, suggesting that the process of cell death involved membrane rupture and loss of cytoplasmic content. Thus, ionophore-induced cell death was a mixture of both necrotic and apoptotic cell death, in accordance with the observation that both pathways are activated by high calcium (7).

**Tamoxifen Does Not Enhance Calcium Signaling among Primary Astrocytes.** In sharp contrast to the tamoxifen-associated enhancement of calcium signaling in breast cancer and glioma, astrocytes derived from both human and rodent brain tissues displayed no significant effect of tamoxifen treatment on calcium signaling (Table 1). Neither the calcium wave radius nor the relative increase in calcium (ΔF/F) differed significantly between tamoxifen-treated astrocytes and their vehicle-treated controls. Similarly, tamoxifen did not significantly increase ATP release from rat astrocytes (Fig. 2). Thus, tamoxifen potentiation of local calcium signaling appeared to be limited to neoplastic breast and glial cells and was not observed in nontransformed astrocytes.

**Discussion**

Tamoxifen is a synthetic antiestrogenic compound widely used to treat breast cancer and has recently been approved for the chemoprevention of breast cancer (8). Tamoxifen is also used as an adjuvant...
The cultures were stained with Hoechst (2 μm calcium ionophore lasalocid (40 μm nuclei). Nuclear fragmentation) and necrosis (arrowhead). Cell death was a mixed pattern of apoptosis (arrow D, cellular shrinkage and 25 min (contrast, most cells pretreated with tamoxifen lost viability when exposed to lasalocid for tamoxifen pretreatment; B—D exposed to tamoxifen alone (B) or lasalocid-exposed cultures (25 min exposure, no tamoxifen pretreatment; C) displayed little injury, and most of the cells were viable. In contrast, most cells pretreated with tamoxifen lost viability when exposed to lasalocid for 25 min (D). Cell death was a mixed pattern of apoptosis (arrow, cellular shrinkage and nuclear fragmentation) and necrosis (arrowhead, cellular “ghost” membranes without nuclei). Bar, 50 μm.

Fig. 4. Tamoxifen increased the sensitivity of C6 glioma cells to calcium ionophore-induced injury. A, cultures were pretreated with tamoxifen (2 h, 10 μM) and exposed to the calcium ionophore lasalocid (40 μM) at increasing time periods (0, 10, 15, 20, 25, 30, 40, and 50 min) and returned to fresh culture medium after three washes. The alamar blue assay was used to quantify glioma viability. Readings were taken 24 h after ionophore exposure. Control cultures (0 min lasalocid exposure) showed no signs of cellular injury and displayed the highest relative absorbance. Lasalocid exposure induced a dose-dependent decrease in relative absorbance, and tamoxifen pretreatment decreased the threshold to ionophore-induced injury. B—D, cultures exposed to lasalocid 24 h earlier. The cultures were stained with Hoechst (2 μM) to display nuclear changes. Cultures exposed to tamoxifen alone (B) or lasalocid-exposed cultures (25 min exposure, no tamoxifen pretreatment; C) displayed little injury, and most of the cells were viable. In contrast, most cells pretreated with tamoxifen lost viability when exposed to lasalocid for 25 min (D). Cell death was a mixed pattern of apoptosis (arrow, cellular shrinkage and nuclear fragmentation) and necrosis (arrowhead, cellular “ghost” membranes without nuclei). Bar, 50 μm.

treatment of several other types of tumors including malignant gliomas (9–11). The action of tamoxifen was initially believed to result from ER interactions, but it is now clear that tamoxifen has mixed agonist and antagonistic effects on the ER and, in addition, many effects that appear independent of steroid-related pathways. For instance, tamoxifen inhibits protein kinase C (12), binds to calmodulin, interferes with the function of both calcium and chloride channels, and possess antioxidant properties (11). Importantly, high concentrations of tamoxifen have been shown to inhibit cell proliferation and to induce apoptosis (10). In this report, we observed that tamoxifen modulated calcium signaling by increasing agonist-induced calcium elevations as well as by accentuating the spatial expansion of calcium waves in both MCF-7 breast cancer cells and several glioma cell lines. Accordingly, tamoxifen has previously been reported to prolong carbachol-triggered intracellular Ca2+ surges in granulosa cells from preovulatory follicles (13). We speculate that the antimitotic action of tamoxifen may be linked to deregulation and spreading of local calcium signals.

Calcium signaling in the form of long-distance calcium waves appears to represent a general mechanism of intercellular signaling among most primary and transformed types studied thus far. The present report adds the existence of propagating calcium waves in breast cancer cells to this list. Calcium signaling is not restricted to cultured cells because intercellular calcium waves have been visualized in intact or semi-intact preparations of brain, heart, pancreas, and liver (14). Although the physiological significance of calcium signaling has not been established, it appears to be critical for proper function and development of most tissue. For instance, astrocytic calcium waves have been shown to modulate forebrain synaptic activity and may represent a mechanism by which astrocytes participate in complex brain function (14). The generation of calcium waves under pathological conditions, such as stroke and trauma, has been causally associated with secondary injury and bystander death, which are both preceded by increments in cytosolic calcium (2).

Calcium waves travel from cell to cell by gap junction-mediated diffusion of Ca2+/inositol 1,4,5-triphosphate, but several recent studies have indicated that calcium waves may also be transmitted by release of ATP and by juxtacrine activation of purinergic receptors (5). The gap junction- and purinergic-mediated signaling pathways coexist in most cell types and can be regulated independently. In this report, we found that tamoxifen selectively enhanced purinergic signaling. Tamoxifen-treated cultures released 3-fold more ATP after stimulation than did control vehicle-treated cultures.

In addition to their role in signaling, extracellular purines have important trophic functions. They stimulate proliferation of MCF-7 breast cancer cells (15) and regulate neurite outgrowth (16). Both MCF-7 and C6 glioma cells are highly responsive to purines and express the P2U receptor (5, 15). Interestingly, it has recently been shown that 17β-estradiol can induce a rapid activation of MAPK in MCF-7 breast cancer cells, promoting cellular proliferation (17). The activation of MAPK by 17β-estradiol is independent of both transcription and protein synthesis but is preceded by a transient increase in cytosolic calcium. Calcium chelation inhibits the activation of MAPK. Thus, estrogen may, in addition to acting by pathways involving receptor-mediated transcription factors, participate in the regulation of both intracellular calcium homeostasis and MAPK-signaling pathways through a nongenomic mechanism (17). Estrogen also enhanced calcium signaling in C6 glioma cells (data not shown), but it remains to be established to what extent the effects of tamoxifen are exercised via estrogen-dependent signaling pathways.

It has been shown previously that nucleotides can act synergistically with polypeptides, hormones, and growth factors such as basic fibroblast growth factor (16). Purinergic receptor activation is asso-
associated with increases of cAMP in several systems, and elevation of cAMP is sufficient by itself to promote the survival of several cell lines. This suggests that cAMP may enhance trophic responsiveness. Indeed, elevation of cAMP in ganglion cells enhances brain-derived neurotrophic factor responsiveness by recruiting the trkB receptor to the plasma membrane (reviewed in Ref. 18). In this regard, the purinergic receptor antagonist suramin inhibits Ca2+- and phospholipid-dependent protein kinase C activity in MCF-7 cells in a dose-dependent manner (19). C6 glioma cells do not express immunoreactive ER receptors (data not shown), in accordance with earlier reports demonstrating that ER mRNA and ER immunoreactivity are undetectable in malignant gliomas (20). It is therefore likely that the tamoxifen-induced enhancement of calcium signaling is not mediated by the “classic” genomic ER pathway but rather by alternative nongenomic pathways.

Calcium signaling might therefore have opposing effects on tumor growth. Purinergic stimulation is associated with an increased rate of proliferation, whereas abnormal calcium signaling promotes tumor cell death. Calcium signaling initiated in the nutrient-deprived centers of rapidly growing tumors may cause secondary injury, similar to the events leading to secondary injury in ischemic stroke (2). Tamoxifen, under ischemic conditions, may prolong and expand calcium increases, thereby increasing tumor cell death. On a cellular level, tamoxifen-induced amplification of agonist- or stress-induced calcium surges may convert sublethal cellular stress to irreversible injury. The observation that tamoxifen lowered the threshold for calcium ionophore-induced cell death (Fig. 4) supports the existence of such a mechanism. Together, these observations may suggest a means for tamoxifen-associated antineoplastic effects by a tamoxifen-triggered, purine-dependent induction of tumor necrosis on a microcellular scale.

References
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