

Tumor Treating Fields Disrupt the Nuclear Envelope to Trigger Immune Response in Glioblastoma

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Abstract

Glioblastoma (GBM) is the most common primary brain tumor. GBM nearly never stops coming back after aggressive treatment. The present course of care for treating GBM has not changed significantly since 2005 until the development of TTFs. Tumor Treating Fields is a novel therapy that employs non-invasive low-intensity electric fields to prevent cancer cells' ability to divide as well as their ability to grow and multiply. This approach to cancer immunotherapy disrupts the nuclear envelope to produce proinflammatory cytokines while inducing inflammation to restrain tumors. Temozolomide (TMZ) is commonly used in chemoradiation therapy and is often used in patients who are newly diagnosed with glioblastoma. Through this experiment we determined and evaluated whether treating glioblastoma cells with TT Fields and temozolomide will successfully and effectively trigger an immune response as well as eliminate glioblastoma cells.

FIGURES

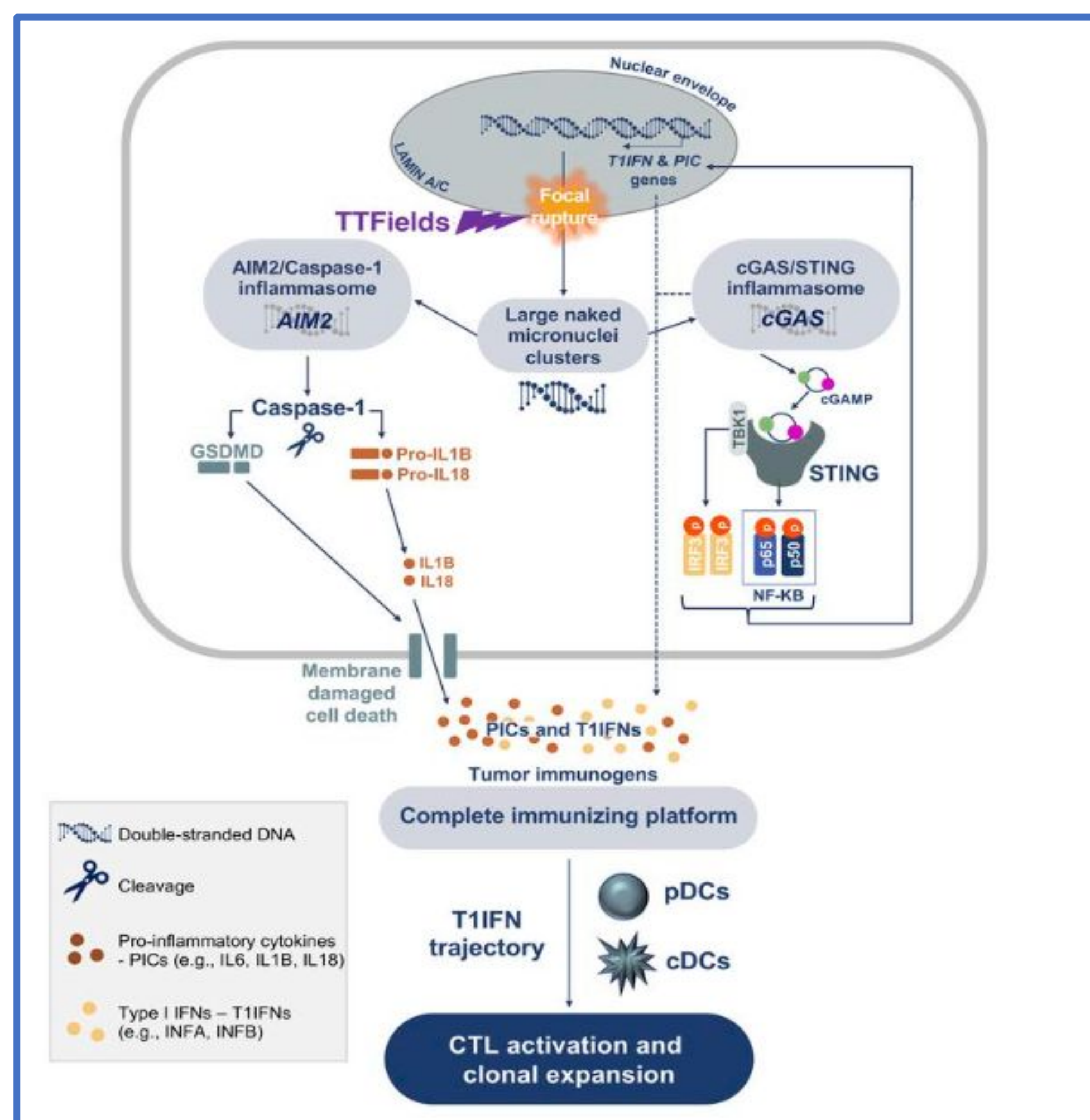


Figure 1: TTF fields may cause inflammation as well although the exact cause of this feature is not clear, nor is it known if it may be used therapeutically. Large micronuclei clusters were released into the cytoplasm after the focal disruption of the nuclear envelope which was caused by TTFs. The cyclic GMP-AMP synthase (cGAS), and AIM2, and their corresponding cGAS/stimulator of interferon genes (STING) and AIM2/caspase 1 inflammasomes were extensively recruited and activated by these clusters. They generate type 1 interferons (T1FNs), proinflammatory cytokines, and T1FN-responsive genes.

FIGURES

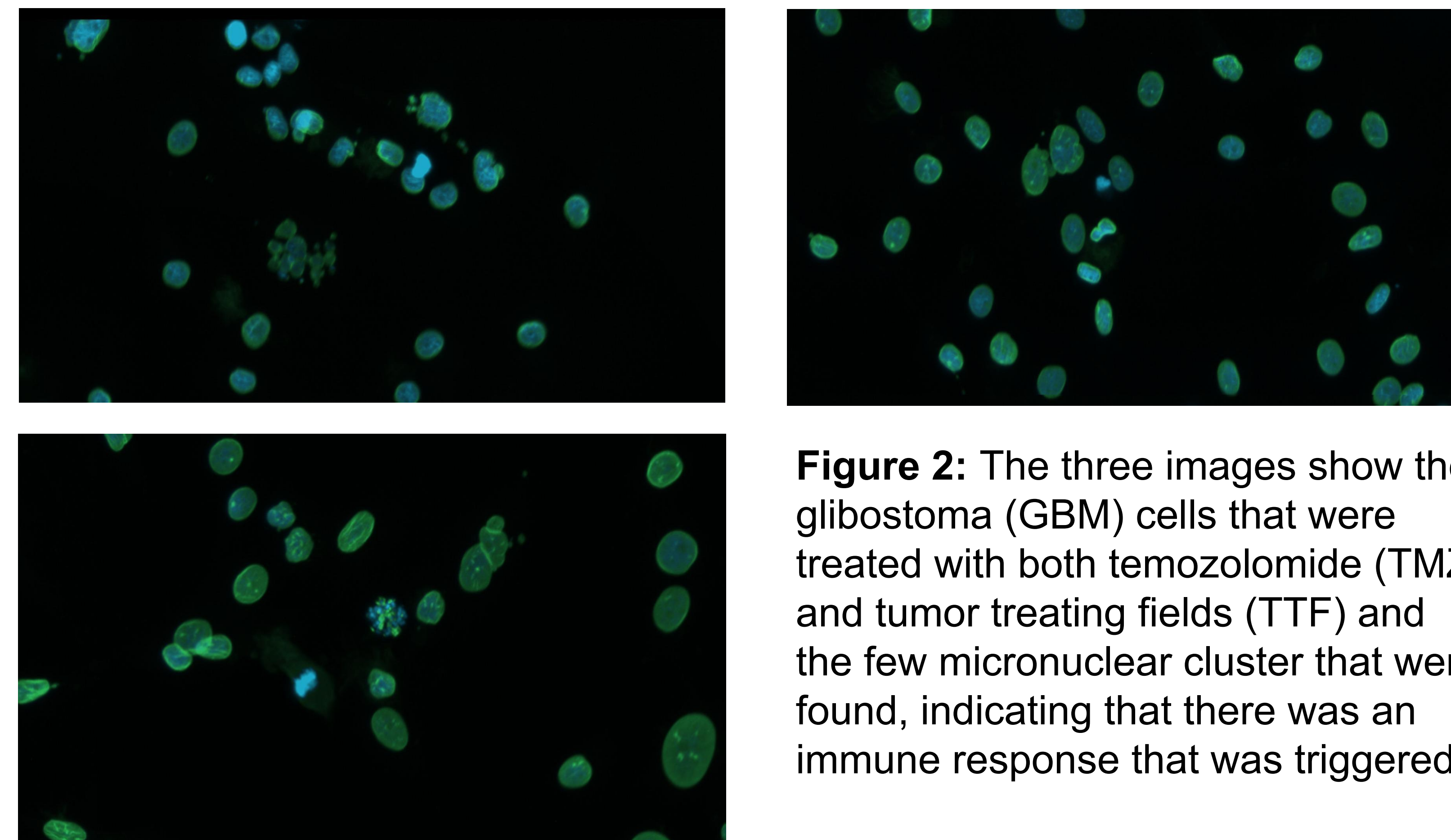


Figure 2: The three images show the glioblastoma (GBM) cells that were treated with both temozolomide (TMZ) and tumor treating fields (TTF) and the few micronuclei clusters that were found, indicating that there was an immune response that was triggered.

FIGURES

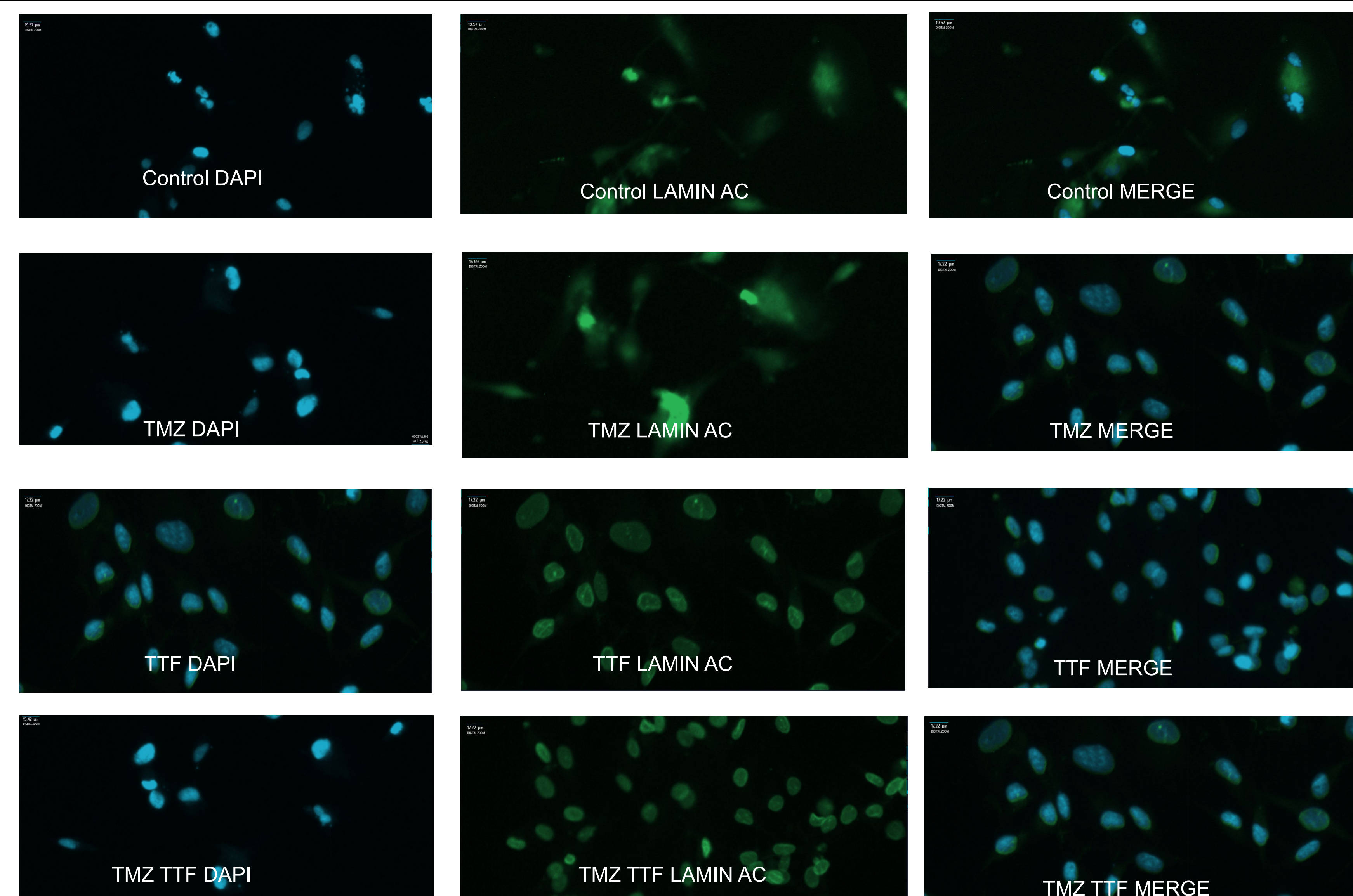


Figure 3: In the figure above the first row shows the control group of cells that were only treated with the vehicle and reagent Dimethyl sulfoxide as well as the cells with only DAPI, which is used to determine the number of nuclei. Lamin AC shows the nuclear envelope, while both dyes together shows the nuclei and nuclear envelope. The second row shows the GBM cells which were treated with both vehicle and TMZ. The third row shows the cells treated with both vehicle and TTFs. The last row shows the cells treated with TMZ plus TTFs.

METHODS & MATERIALS / RESULTS

METHODS & MATERIALS

The data collection of this study was divided into several parts. First, we passaged GBM cells (U87) and counted the number of cells we had. Second, we permeabilized the membrane of the cells using a buffer solution of 0.2 Triton. After incubating the cells, we added the primary antibodies (anti-Lamin AC & DAPI). To prepare the cells for imaging, we washed the cover slip with PBR solution three times and sealed it with slide glue. We passaged the cells and divided them into 2 controls, 2 treated with tumor treating fields and 2 treated with temozolomide. We stained the cells with DAPI first and then we stained the cells with Lamin AC. After that we used a semi-automated imaging system (Image Xpress Pico) to take images of each group of cells with fluorescence microscopy to examine the release of micronuclei clusters.

RESULTS

Our results show that there were a small number of nuclei that were separated from the nuclear envelope, in the cells that were treated with TTF only, and TMZ + TTF, indicating an immune response in all of them.

Summary

Although we could not determine what percentage of micronuclei clusters indicate how effective the treatment is, we did observe the cells treated with both temozolomide and tumor treating fields showed the most frequent release of micronuclei clusters which indicate the immune response in the body being triggered. As stated, before the release from the nuclear envelope due to disruption was found in treatments with tumor treating fields, We have also found that as the dosage of the treatment increases, less GBM cells are present. Further research is needed for more quantitative data.

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