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Using Lysosomal Immunogenic Cell Death to Target Breast Cancer via Xanthine Oxidase/Micro-Antibody Fusion Protein

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Abstract : Lysosome-induced immunogenic cell death (LIICD) is a powerful mechanism of targeting cancer cells that kills circulating malignant cells and primes the host's immune cells against future remission. Current immunotherapies for cancer are limited in preventing recurrence – a gap that can be bridged by training the immune system to recognize cancer neoantigens. Lysosomal leakage can be induced therapeutically to traffic antigens from dying cells to dendritic cells, which can later present those tumorigenic antigens to T cells. Previous research has shown that oxidative agents administered in the tumor microenvironment can initiate LIICD. We generated a fusion protein between an oxidative agent known as xanthine oxidase (XO) and a mini-antibody specific for EGFR/HER2-sensitive breast tumor cells. The anti-EGFR single domain antibody fragment is uniquely sourced from llama, which is functional without the presence of a light chain. These llama micro-antibodies have been shown to be better able to penetrate tissues and have improved physicochemical stability as compared to traditional monoclonal antibodies. We demonstrate that the fusion protein created is stable and can induce early markers of immunogenic cell death in an in vitro human breast cancer cell line (SkBr3). Specifically, we measured overall cell death, as well as surface-expressed calreticulin, extracellular ATP release, and HMGB1 production. These markers are consensus indicators of ICD. Flow cytometry, luminescence assays, and ELISA were used respectively to quantify biomarker levels between treated versus untreated cells. We also included a positive control group of SkBr3 cells dosed with doxorubicin (a known inducer of LIICD) and a negative control dosed with cisplatin (a known inducer of cell death, but not of the immunogenic variety). We looked at each marker at various time points after cancer cells were treated with the XO/antibody fusion protein, doxorubicin, and cisplatin. Upregulated biomarkers after treatment with the fusion protein indicate an immunogenic response. We thus show the potential for this fusion protein to induce an anticancer effect paired with an adaptive immune response against EGFR/HER2+ cells. Our research in human cell lines here provides evidence for the success of the same therapeutic method for patients and serves as the gateway to developing a new treatment approach against breast cancer.

Keywords : apoptosis, breast cancer, immunogenic cell death, lysosome
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