Background

High densities of tumor-infiltrating lymphocytes (TILs) in triple-negative breast cancer (TNBC) are associated with better outcomes and response to checkpoint blockade therapy (CBT). However, only ~20% of TNBC contain elevated TIL, and only ~20% of treatment naïve TNBC patients respond to CBT as a monotherapy; thus, approaches are needed to increase TIL and to enhance efficacy of CBT. CXCL10 is a critical chemoattractant for activated T cells, but it is found in only 17% of breast cancers. Thus, approaches to increase CXCL10 may boost TIL and enhance CBT efficacy. We hypothesized that a combination therapy of a TLR2 agonist and IFNγ would enhance CXCL10 production, TIL, and tumor control in TNBC.

Methods

12 human TNBC cell lines were evaluated by flow cytometry and ELISA post stimulation with TLR2 agonist (FSL-1), IFNγ, Sham, or FSL-1+IFNγ for CXCL10 production; and 3 murine TNBC cell lines were evaluated by ELISA assay.

The E0771-TNBC model was utilized to evaluate the impact of FSL-1 and IFNγ on T-cell infiltration and tumor growth. 1.5x10^5 E0071 cells were injected into the mammary fat pad of C57BL/6J mice and allowed to grow for 23 days to ~400 mm^3 in size. Tumors were injected with PBS, 50 μg FSL-1, 10,000 units IFNγ, or FSL-1+IFNγ, on days 23 and 26 and evaluated for T-cell infiltrates.

Results

We found that most human TNBC cell lines produced little CXCL10 after IFNγ stimulation alone. However, FSL-1 +IFNγ stimulation significantly increased CXCL10 production from human and murine TNBC cell lines, when compared to IFNγ alone (p<0.001 and p<0.03, respectively). Furthermore, in mice containing E0771-TNBC, intratumoral administration of FSL-1+IFNγ enhanced T-cell infiltrates and reduced tumor growth, when compared to IFNγ or FSL-1 treatment alone (p≤0.03).

Conclusions

Most human TNBC have defects in production of CXCL10, likely mediated by defects in response to IFNγ. This suggests that an additional stimulus is needed to promote CXCL10 production by TNBC cells. We have identified synergy between a TLR2 agonist (FSL-1) and IFNγ in promoting CXCL10 production by TNBC cells. Additionally, in vivo data reveal that FSL-1+IFNγ treatment increases TIL and tumor control. Understanding the mechanism for the varied production of CXCL10 by TNBC cells in response to IFNγ and TLR2 stimulation, will bring insight into the regulation of CXCL10 production in TNBC, and how to optimize this to enhance TIL engagement and tumor control.

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