Background
Due to its aggressive behavior and frequent development of chemotherapy resistance, triple negative breast cancer (TNBC) is the most lethal subtype of breast cancer. Although natural killer (NK) cell-based immunotherapy is a promising strategy for overcoming treatment barriers, the therapeutic efficacy of NK cells against TNBC falls short of expectations. ELK3, an E26 transformation-specific transcription factor, is highly expressed in TNBCs and acts as a master regulator of the epithelial-mesenchymal transition.

Methods
Two representative human TNBC cell lines, MDA-MB231 and Hs578T, were engineered with ELK3-targeting shRNA or ELK3-expressing plasmid. A combination of gene expression profiling and molecular analysis was used to identify ELK3’s downstream target genes. The role of ELK3 in determining TNBC immunosensitivity to NK cells was studied in vitro and in vivo in terms of mitochondrial fission-fusion transition and reactive oxygen species concentration. With syngeneic mouse model of Elk3 knockout 4T1 cells, tumor infiltrated immune cells were analyzed.

Results
The status of ELK3-dependent mitochondrial fission-fusion in TNBCs was linked to the concentration of mitochondrial superoxide and was a major determinant of NK cell-mediated immune responses. In TNBCs, we discovered that mitochondrial dynamics proteins of 51 (Mid51), a major mediator of mitochondrial fission, is a direct downstream target of ELK3. In addition, we found that ELK3 expression correlated inversely with Mid51 expression, and that the ELK3-Mid51 axis is directly related to mitochondrial dynamics and immune response to NK cells. With a syngeneic mouse TNBC model, we found that ELK3 expression in TNBC is associated with a landscape of immune cells derived from both innate and adaptive immunity that infiltrate the tumor.

Conclusions
Taken together, these findings suggest that ELK3 in TNBCs regulates mitochondrial dynamics, which is directly linked to tumor immunosensitivity. Targeting ELK3 in TNBCs is anticipated to shed new light on strategies for improving the efficacy of NK cell-based immunotherapy for TNBC (figure 1).

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REFERENCES

Ethics Approval
All animal works were approved by the Institutional Animal Care and Use Committee of the laboratory animal research center at CHA University. Primary natural killer cells were isolated from peripheral blood mononuclear cells obtained from healthy donors. This research was reviewed and approved by the institutional review board of CHA University.

Consent
All healthy blood donors provided informed consent.