Supplemetary Figure Legends

(Fig.S1 – S8)

Fig.S1 ScRNA-seq data analysis of TNBC dataset

(A and B) T-SNE plot of all the single cells, each color coded for (A) samples origin and (B) major cell types. (C) Hexbin plot of the marker genes of each cell type. The colors from purple to yellow indicate the gene expression levels from low to high. (D) Heatmap plot of the top 10 marker genes among major cell types. The colors from grey to red indicate the gene expression levels from low to high.

Fig.S2 ScRNA-seq data analysis of HR^+ and $HER2^+$ breast cancer datasets

(A and B) T-SNE plot of all the single cells, each color coded for (A) samples origin and (B) major cell types. (C) Bubble plot of the marker genes of each cell type. The colors from grey to blue indicate the gene expression levels from low to high. (D) T-SNE plot of NKT/NK cells, each color coded for cell types. (E) Heatmap plot of the top 10 marker genes among major cell types. The colors from grey to red indicate the gene expression levels from low to high.

Fig.S3 ScRNA-seq data analysis of integrated NK cells from TNBC, $HR^{+,}$ and $HER2^+$ breast cancer datasets and Kaplan–Meier overall survival curves for respective NK cell clusters.

(A and B) T-SNE plot of all the single cells, each color coded for (A) cell clusters and (B) major cell types. (C and D) Hexbin plot of the top indicated genes among NK cell clusters. The colors from purple to yellow indicate the gene expression levels from low to high. (E) Kaplan–Meier curves of overall survival by stratifying the patients by high and low proportion of the respective cell type.

Fig.S4 Isolation of NK cells from breast cancer tissues and PBMCs, and qPCR assay for detecting *UGDH-AS1* expression in NK cells.

(A and B) Representative dot plot of NK cells gating ($CD3^-CD56^+$) in PBMC (A) and breast cancer tissues (B). (C) The expression of *UGDH-AS1* in TNBC ($n = 47$), HR^+ breast cancer ($n = 29$), and $HER2^+$ breast cancer ($n = 33$). (D) The expression of *UGDH-AS1* in TNBC and PBNK ($n = 10$). (mean ± SD, $*p<0.05$; $**p<0.01$ and $***p<0.001$).

Fig.S5 The relationship among IFN-γ, GZMB, PRF1, *UGDH-AS1* and the *UGDH-AS1* encoding micropeptide.

(A) The proliferation of indicated NK-92MI cells were determined by EdU assays ($n = 5$) (left). The apoptosis of indicated NK-92MI cells were monitored by Annexin V staining ($n = 3$) (right). (B) Cytotoxic activity of *UGDH-AS1* overexpressed and control NK-92MI cells against Hs578T cells ($n = 3$). (C) Relative abundance of *UGDH-AS1* transcript in nucleus and cytoplasm fractions from NK-92MI cells. *GAPDH* and *U6* were used as cytoplasmic and nuclear controls respectively. (D and F) NK-92MI cell lysates were fractionated to collect non-ribosome, 40S-80S and polysome fractions by

sucrose gradient centrifugation. HPRT1 (D), circHIPK3 (E) and *UGDH-AS1* (F) in these fractions were quantified by qPCR. (H) The expression of *UGDH-AS1* encoding micropeptide and *UGDH-AS1* in NK-92MI or PBNK cells with/without *UGDH-AS1* overexpressing. (I) Immunofluorescence with anti-micropeptide in TINK and PBNK cells. (mean ± SD, NS, no significance, *p<0.05; **p<0.01 and ***p<0.001).

Fig.S6 Generation of *NKSM*$^{+/+}$ mice.

(A) Schematic diagram of NKSM conditional knock-in strategy. (B) The expression of NKSM in wild-type or transgene mice. (C) Absolute numbers and percentage of NK cell within each organ of the indicated mice (n = 5). (D) In vivo proliferation of splenic NK cells. Mice were injected intraperitoneally with EdU (200 μg). After 12 h, the incorporation of EdU in splenic NK cells of indicated mice was analyzed by flow cytofluorimetric analysis (n = 5). (E) Purified splenic NK cells were cultured in media without IL-2 for 6 h. The viability was monitored by Annexin V staining (n = 5). (mean ± SD, NS, no significance).

Fig.S7 Transcriptional factor binding sites prediction, correlation analysis of *UGDH-AS1* and *TBX21*

(A) The predicted binding sites of SMAD2/3/4 at *UGDH-AS1* promoter. (B) The canonical SMAD2/3/4-binding motif (JASPAR Database). (C) The predicted binding sites of c-Myc at *TBX21* promoter. (D) The canonical c-Myc-binding motif (JASPAR

Database). (E) Schematic diagram illustrating the 2 200 bp upstream and 300 bp downstream (A-E) regions of the *TBX21* promoter. (F) Schematic diagrams of luciferase reporter constructs with wild-type and mutant *TBX21* promoter. (G) The expression of IFN-γ, GZMB and PRF1 were controlled by both c-Myc and T-bet. NK cells were culture with TGF-β and IL-12/IL-15 for 1 day.

Fig.S8 *NKSM* knockout and *NKSM* was a potential target in TNBC immunotherapy.

(A) Schematic diagram of *NKSM* knockout strategy. (B) The mRNA level of *NSKM* in wild-type (WT) or NKSM knockout (KO) NK-92MI cells treated with TGF-β for 1 day (n = 3). (C) The expression of NKSM in WT or NKSM knockout NK-92 cells treated with TGF-β for 1 day. (D) Cytotoxic activity of NKSM knockout and wild-type NK-92MI cells towards K562 cells in the culture medium of Hs578T cells (n = 3). (E) NKSM knockout enhanced the NK cells induced TNBC tumor regression in the xenografts NCG mice. Six-week-old female NCG mice were injected subcutaneously in the left side with MDA-MB-231 cells until the tumors volume reached ~100mm^3. The mice were then randomly grouped and intravenously injected with indicated cells twice a week for 4 weeks (n = 5). (mean ± SD, NS, no significance, *p<0.05; **p<0.01 and ***p<0.001).