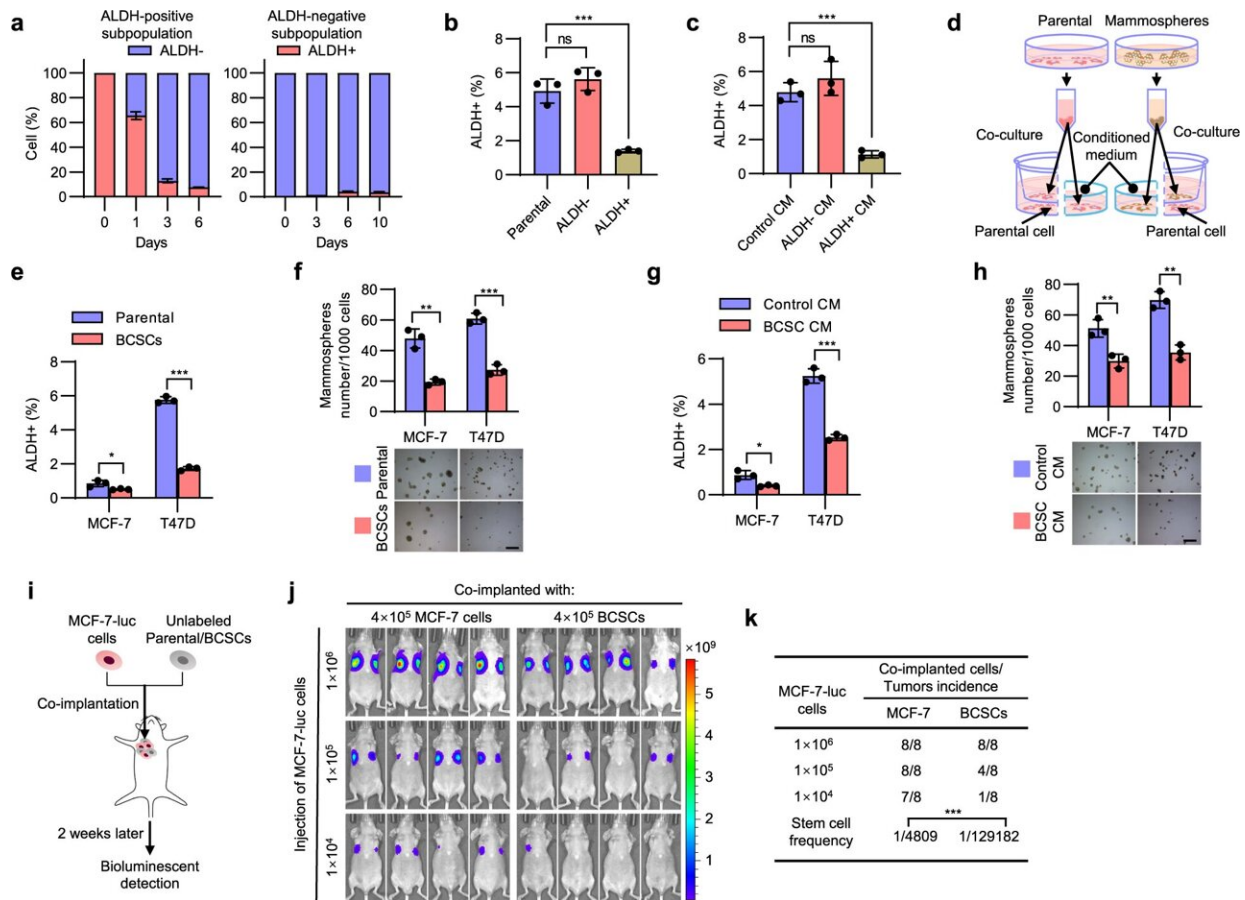


# Researchers identify ways to limit transferred cancer growth

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BCSC secretome compresses the stem cell pool size. a FACS analysis of the proportion of ALDH+ or ALDH- cells after the growth of FACS-sorted ALDH+ or ALDH- T47D cells. b FACS analysis of the proportion of ALDH+ BCSCs in the RFP-labeled T47D cells co-cultured with the unlabeled ALDH-, ALDH+ or parental T47D cells. c FACS analysis of the proportion of ALDH+ BCSCs in the T47D cells cultured with the CM derived from ALDH+, ALDH-, or parental cells. d The schematic of conditioned medium and transwell co-

culture system. e, f MCF-7 or T47D cells were co-cultured with mammosphere-enriched BCSCs or parental cells for 48 h, and the stemness properties were subsequently analyzed by ALDEFLUOR assay (e) or mammosphere-formation assay (f). Scale bars: 500  $\mu\text{m}$ . g, h MCF-7 or T47D cells were cultured with the respective CM derived from mammosphere-enriched BCSCs or parental cells for 48 h, and the stemness properties were subsequently analyzed by ALDEFLUOR assay (g) or mammosphere-formation assay (h). Scale bars: 500  $\mu\text{m}$ . i The schematic of co-implantation model. j, k A series of limiting diluted MCF-7-luc cells were co-implanted with unlabeled  $4 \times 10^5$  mammosphere-enriched BCSCs or parental cells into host mice. Bioluminescent imaging (BLI) was performed on tumors generated by MCF-7-luc cells (j), the CSC frequency was calculated using ELDA software (k). Results are shown as mean  $\pm$  S.D. \*P less than 0.05; \*\*P less than 0.01; \*\*\*P less than 0.001; ns not significant (One-way ANOVA followed by Tukey's multiple comparison test in (b, c) others unpaired two-tailed Student's t test). Credit: *Nature Communications* (2022). DOI: 10.1038/s41467-022-29018-9

Cancer stem cells (CSCs), a key driver behind malignant cancer progression, are self-renewing, highly metastatic and therapeutically resistant. As cancer progresses, cancer cells display a phenotypic plasticity between the stem-like and differentiated subpopulations, each of which can reestablish the composition of parental cells. The mechanism and functions of this plasticity, however, remain largely unknown.

In a study published in *Nature Communications*, a research team led by Prof. Zhu Tao from the University of Science and Technology of China (USTC) of the Chinese Academy of Sciences unveiled the role of CSC-regulated phenotypic plasticity in metastatic colonization.

The researchers designed co-culture systems in vitro and co-implantation systems in vivo. Based on these systems, they found that breast [cancer](#)

[stem cells](#) (BCSCs) inhibit their own capacity through the BSCS-derived secretome. By means of screening, bioluminescent imaging and others, they also found that DKK1 plays a pivotal role in the secretome. DKK1 was identified as a pivotal molecule that autonomously diminishes the CSC population and subsequently promotes [breast cancer](#) metastatic colonization.

Further experiments showed that this autonomous restraint of BCSCs can prompt disseminated [tumor cells](#) (DTCs), which remain largely dormant after arriving at distant sites, to exit from dormancy and then achieve metastatic colonization. A small-molecule inhibitor of the DKK1, however, can achieve a nearly complete blockade of lung metastasis in many BCSC metastasis models.

Ferroptosis, a non-apoptotic cell death process, is caused by abnormal metabolism and lipid peroxidation. Compared with those in primary mammary cancers, [cancer cells](#) from lung metastases are under higher oxidative and ferroptotic stress. The researchers revealed that the highly invasive CSCs have a relatively high concentration in lung metastases, where CSCs can secrete DKK1 that restrain CSCs. As CSCs are highly sensitive to ferroptosis, CSC-secreted DKK1 protects cells in lung metastases from ferroptosis and thus contributes to metastatic outgrowth.

The findings of this study reveal the role of CSC-regulated [phenotypic plasticity](#) in metastatic colonization, and provide new therapeutic approaches to effectively inhibit metastases.

**More information:** Mingming Wu et al, Cancer stem cell regulated phenotypic plasticity protects metastasized cancer cells from ferroptosis, *Nature Communications* (2022). [DOI: 10.1038/s41467-022-29018-9](https://doi.org/10.1038/s41467-022-29018-9)

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