**Adherent-to-suspension transition, circulating tumor cells, and anti-metastatic therapy**

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**Abstract**

Background & Objectives

Although metastasis is the foremost cause of cancer-related death, a specialized mechanism that reprograms anchorage dependency of solid tumor cells into circulating tumor cells (CTCs) during metastatic dissemination remains a critical area of challenge.

Methods

We analyzed blood cell-specific transcripts and selected key Adherent-to-Suspension Transition (AST) factors that are competent to reprogram anchorage dependency of adherent cells into suspension cells in an inducible and reversible manner. The mechanisms of AST were evaluated by a series of in vitro and in vivo assays. Paired samples of primary tumors, CTCs, and metastatic tumors were collected from breast cancer and melanoma mouse xenograft models and patients with de novo metastasis. Analyses of single-cell RNA sequencing (scRNA-seq) and tissue staining were performed to validate the role of AST factors in CTCs.

Results

We discovered a biological phenomenon referred to as AST that reprograms solid tumor cells into CTCs via defined hematopoietic transcriptional regulators. Induction of AST in solid tumor cells 1) suppress global integrin/ECM gene expression via Hippo-YAP/TEAD inhibition to evoke spontaneous cell-matrix dissociation and 2) upregulate globin genes that prevent oxidative stress to acquire anoikis resistance. During dissemination, we uncover the critical roles of AST factors in CTCs derived from patients with de novo metastasis and mouse models. Pharmacological blockade of AST factors via thalidomide derivatives abrogated CTC formation and suppressed lung metastases.

Conclusion

We demonstrate that suspension cells can directly arise from adherent cells by the addition of defined hematopoietic factors that confer metastatic traits. Furthermore, our findings expand the prevailing cancer treatment paradigm toward direct intervention within the metastatic spread of cancer.

Selected publications

1. Mol Cancer. 2023 Mar 30;22(1):63. doi: 10.1186/s12943-023-01753-7.

2. Mol Cancer. 2023 Nov 6;22(1):177. doi: 10.1186/s12943-023-01837-4.

3. Biotechnol J. 2024 May;19(5):e2400104. doi: 10.1002/biot.202400104.

4. Nat Comm. In review

**Do you have any conflicts of interest?**

No, I do not have a conflict of interest.