Reprogramming anchorage dependency by adherent-to-suspension transition promotes metastatic dissemination

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Study Aim: To investigate the mechanism by which solid tumor cells reprogram their anchorage dependency to become circulating tumor cells (CTCs) during metastatic dissemination.

Methods:

- Transcriptome analysis of adherent and suspension cell lines
- In vitro experiments with genetically modified cell lines
- Mouse xenograft models of breast cancer and melanoma
- Single-cell RNA sequencing of patient-derived and mouse model-derived CTCs
- Immunohistochemistry of patient samples
- Loss-of-function experiments using shRNA knockdown and pharmacological inhibition

Key Findings:

- Identified four key transcription factors (IKZF1, NFE2, BTG2, and IRF8) that induce Adherent-to-Suspension Transition (AST)
- AST factors suppress cell-matrix adhesion genes via YAP-TEAD inhibition and upregulate globin genes for anoikis resistance
- AST factors are expressed in CTCs but not in primary tumors or metastases
- Blocking AST factors reduced CTC formation and metastasis without affecting primary tumor growth
- Thalidomide derivatives, which target IKZF1, showed potential as anti-metastatic agents

Conclusions:

- AST is a novel mechanism by which solid tumor cells reprogram their anchorage dependency to become CTCs
- Solid tumor cells hijack hematopoietic transcription factors (AST factors) to enable their dissemination as CTCs
- AST factors represent promising therapeutic targets for preventing metastasis
- This study expands the cancer treatment paradigm towards directly intervening in the metastatic spread of cancer

The study uncovers a novel mechanism called Adherent-to-Suspension Transition (AST) that enables cancer cells to become circulating tumor cells, promoting metastasis and offering new targets for anti-metastatic therapies.

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- **Analyzation of patient's tissue/blood samples**

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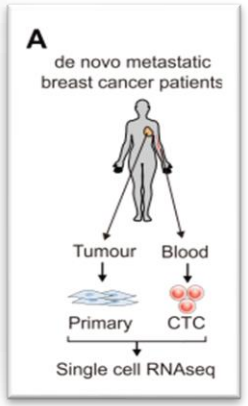

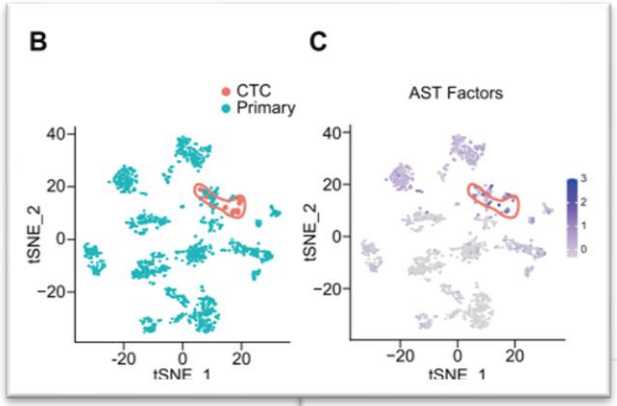

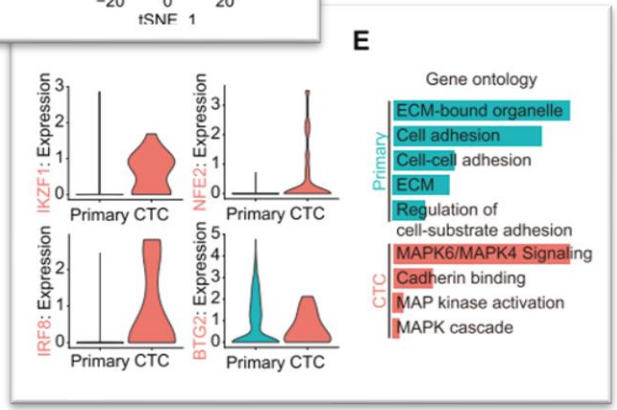

- ➢ **Study of Adherent-to-Suspension Transition (AST) factors in CTC**
- ➢ **de novo metastatic breast cancer patients' tissue/blood sample**
- ➢ **Identified increased AST factors (IKZF1, IRF8, NFE2, BTG2)**
- ➢ **Targeting AST factors can block CTC generation/metastasis independent of primary tumor growth**

Discovery of new biomarkers and biological phenomenon

The research conducted by Professor Hyunwoo Park of the AST Research Group at Yonsei University is exploring the molecular mechanisms of cancer metastasis in a mouse model using Cytogen's platform.

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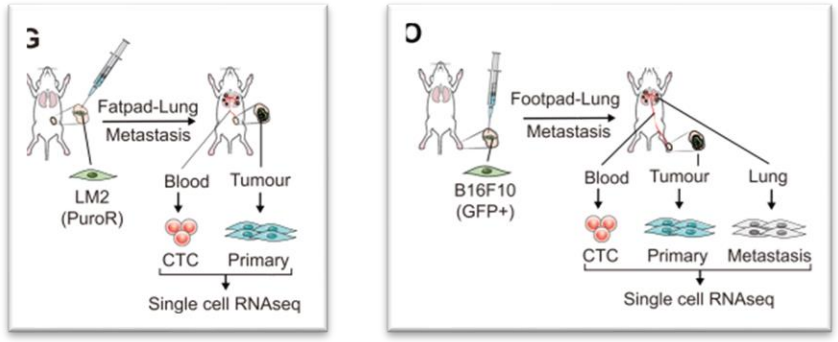
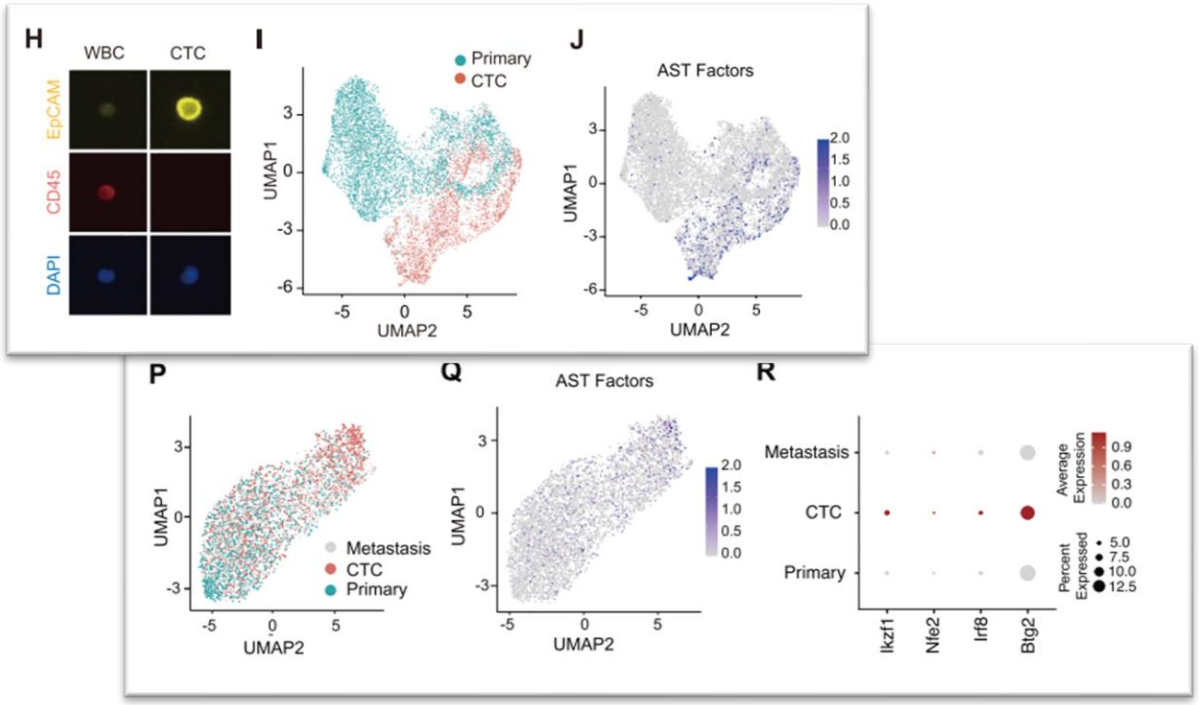
- **Using CytoGen's HDM chip for CTC detection in Orthotopic model**



- **Isolated CTC Analyzation using IF staining and transcriptomes**



- **Utilized in preclinical animal model research.**
- **Able to isolate live CTCs from an orthotopic model.**
- **Proposes new therapeutic strategies.**