Two distinct epithelial-to-mesenchymal transition programs control invasion and inflammation in segregated tumor cell populations

Presenter : Jing-Ru Chen
Commentator : Hsiang-Chi Huang, Ph.D
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Background:
Epithelial-to-mesenchymal transition (EMT) is an important biological process that controls cell plasticity during development, tissue repair, and cancer. Instead of being a simple switch between epithelial and mesenchymal states, EMT represents a spectrum of hybrid E/M states with distinct functional outcomes. In cancer, these different EMT states can influence how cells invade, cause inflammation, and form metastases. However, how these various EMT programs coexist and interact inside tumors is still not well understood.

Objective:
This study aimed to explore the molecular diversity of EMT in different biological contexts, including development, fibrosis, and cancer. By combining cell-line models, neural-crest EMT, renal fibrosis, and breast-cancer single-cell transcriptomics , the authors tried to delineate distinct EMT pathways, identify their key regulators, and how each pathway contributes to invasion, inflammation, and immune modulation in the tumor microenvironment.

Results:
The researchers discovered two main EMT programs in cancer cells that are connected but functionally different. The first program, called EMT-T1, is similar to embryonic EMT and promotes invasion and metastasis. The second program, EMT-T2, is more like adult tissue EMT and is related to inflammation and immune modulation. Both programs are triggered by the transcription factor SNAIL1, which represses epithelial genes to start EMT. However, PRRX1 specifically maintains the invasive EMT-T1 state. When PRRX1 knockout, metastasis is reduced, but inflammatory gene expression increases, shifting cells toward the EMT-T2 program. This shows that EMT is not a single linear process but a flexible network that changes in response to signals from the environment. Supporting experiments showed that PRRX1 knockdown in TGF-β–treated MDCK cells blocked complete EMT and invasion, renal fibrosis models demonstrated SNAIL1-dependent inflammatory EMT, and PyMT breast cancer models confirmed bifurcation into EMT-T1 and EMT-T2 branches at the single-cell level.

Conclusion:
Overall, these findings uncover a dynamic equilibrium between invasion and inflammation, orchestrated by the SNAIL1–PRRX1 axis. These findings highlight the plasticity of EMT as a key factor in tumor heterogeneity and suggest possible new targets for therapies that selectively block certain EMT programs.