演講題目:

Regulatory intratumoral heterogeneity and triple-negative breast cancer

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摘要:
Triple-negative breast cancer is characterized by poor prognosis and high intratumoral heterogeneity. Using a basal-like breast epithelial line, we have identified two anti-correlated gene-expression programs that arise among single extracellular matrix (ECM)-attached cells during organotypic 3D culture. The first program contains multiple TGFβ-related genes including *TGFBR3*, and its heterogeneous induction is critical to suppress ductal branching during 3D culture. The second program contains *JUND* together with the basal-like marker, *KRT5*. Homogenizing *JUND* expression in single cells leads to 3D acini with bridged lumina that are similar to cribiform ductal carcinoma *in situ*. *TGFBR3* and *JUND* together comprise a circuit that is interconnected via four negative-feedback loops. The *TGFBR3–JUND* circuit and its ECM-dependent regulation are remarkably conserved in early basal-like tumors that heterogeneously express KRT5. The circuit depends on ECM engagement, as detachment causes a rewiring that is maintained by tenascin C, which is critical for intraductal colonization of basal-like breast cancer cells *in vivo*. Breast tumor heterogeneity need not stem from partial basal-like differentiation and could instead reflect dynamic toggling of individual cells between expression states.