

Molecular Gatekeeping of Epithelial Identity in Cancer Progression and Therapeutic Resistance

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Cancer therapeutic response and resistance are governed by both oncogenic driver dependencies and adaptive changes in cancer cell state. The importance of driver identification is illustrated by our characterization of an actionable out-of-frame CBX3::ALK fusion in metastatic melanoma. Beyond oncogenic drivers, a longitudinal model of sustained therapeutic stress revealed sequential inflammatory, epithelial-mesenchymal, hypoxic, and metabolic states during the development of resistance. Within this continuum, STAT1 Lys637 acetylation emerged as a therapy-induced adaptation that attenuates interferon signaling and compromises subsequent response to immune checkpoint blockade. The emergence of an epithelial-mesenchymal program during adaptation supports a model in which resistance develops through a continuum of plastic cell states. Building on our previous studies of epithelial plasticity, the main focus of this talk is the molecular regulation of the hybrid epithelial/mesenchymal state. Our current work identifies GATA3 as a gatekeeper of epithelial identity. An EXOC7 isoform switch promotes PRPF19-dependent GATA3 degradation, while GATA3 acetylation sustains BRD4-P-TEFb-dependent transcription. Disruption of this regulatory circuit destabilizes epithelial identity and promotes invasive partial EMT. These findings reveal how molecular gatekeeping of hybrid cell states shapes cancer progression and therapeutic resistance.