Kidney Cancer

Major Finding: Lineage factor PAX8 is essential for downstream oncogenic signaling of ccRCC-specific driver mutations.

Concept: PAX8 promotes oncogenic signaling through a chromosome 11 germline variant or HIF2A recruitment to a transcriptional enhancer.

Impact: Lineage-specific transcription factors mediate tissue-specific cancer risk and can serve as therapeutic targets.

ONCOGENIC SIGNALING IN KIDNEY CANCER REQUIRES RENAL LINEAGE FACTOR PAX8

Somatic mutations in cancer driver genes generally occur in a tissue-specific manner, suggesting that transcriptional networks required for normal tissue function may also be necessary for oncogenic processes. It remains unknown, however, if interactions between genetic alterations and lineage-specific factors are required to establish cancer type–specific oncogenic programs. Patel and colleagues, using loss-of-function CRISPR screens, identified the dependence of clear-cell renal cell carcinoma (ccRCC) on the renal transcription factors paired box 8 (PAX8) and HNF1B, which when inhibited were found to reduce chromatin accessibility. Parallel analyses also revealed a colocalization of PAX8 and hypoxia-inducible factor 2α (HIF2A) on chromatin more frequently than what would occur by chance, suggesting the interaction of these two proteins at the chromatin level. PAX8 depletion, but not depletion of HNF1B, downregulated the hypoxia gene signature, and investigation into gene regulatory elements that mediate HIF2A-driven ccRCC tumor formation revealed the strongest hit to be an enhancer region within chromosome 11 (E11:69419). Localization of both HIF2A and PAX8 at this loci drives the expression of oncogenic *CCND1* (Cyclin D1), a positive regulator of the cell cycle. Moreover, a germline variant at 11q13.3 common in ccRCC, rs7948643, falls specifically within the PAX8 binding motif that is critical for E11:69419 activity, and PAX8 demonstrated a much higher binding affinity for the rs7948643 risk allele, which in turn yields the enhanced activation of oncogenic Cyclin D1. Additionally, it was shown that PAX8 inhibition decreases ccRCC proliferation, which does not occur upon HIF2A inhibition, suggesting a HIF2A-independent oncogenic function of PAX8. Specifically, PAX8 exhibited positive regulation of *HNF1B* expression, with both PAX8 and HNF1B driving protumorigenic *MYC* expression. Furthermore, a CRISPRi screen identified two distal *MYC* enhancers activated by HNF1B in both normal and malignant renal cells. In summary, this study reveals that the renal transcription factor PAX8 is required for the downstream oncogenic signaling of ccRCC driver mutations, supporting that lineage-specific transcription factor activity can mediate both oncogenic signaling and tissue-specific cancer risk associated with specific genetic variants. ■

Patel SA, Hirosue S, Rodrigues P, Vojtasova E, Richarson EK, Ge J, et al. The renal lineage factor PAX8 controls oncogenic signalling in kidney cancer. Nature 2022;606:999–1006.

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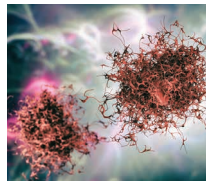
Melanoma

Major Finding: Aged lung fibroblasts promote reactivation of dormant melanoma cells by secreting a WNT antagonist.

Concept: A shift from high to low WNT5A expression allows reactivation following initial dissemination.

Impact: This study sheds light on the phenotypic switch that governs emergence from melanoma dormancy.

AGED LUNGS ENABLE METASTATIC OUTGROWTH OF DORMANT MELANOMA CELLS



Tumor dormancy describes the phenomenon in which cancer cells disseminate from a primary tumor to distant sites, remaining in a nonproliferative dormant state for up to many years before forming overt metastases. Although clinical management of melanoma has been greatly improved by immunotherapy and targeted therapy, metastatic relapse is common, while mechanisms regulating melanoma tumor dormancy and metastatic reactivation are not fully understood. To address this, Fane and colleagues studied a metastasis model in which murine melanoma cells were intradermally transplanted into young (8 weeks) or aged (over 52 weeks) mice, demonstrating that despite similar rates of dissemination proliferative overt metastases occurred only in the lungs of aged mice. Coculture assays suggested that aged murine lung fibroblasts generate a permissive microenvironment for metastatic outgrowth. Moreover, proteomic analysis indicated that aged fibroblasts had significantly higher levels of secreted frizzled related protein 1 (SFRP1), a noncanonical WNT antagonist, and administration of an anti-SFRP1 neutralizing antibody abrogated metastatic outgrowth in aged mice, suggesting the importance of WNT signaling in sustaining a dormant metastatic phenotype. Given studies establishing the role of WNT5A in promoting prostate tumor dormancy, clinical melanoma samples from The Cancer Genome Atlas were stratified based on *WNT5A* expression, revealing that high *WNT5A* expression in melanoma was associated with high expression of dormancy markers and low expression of proliferative markers. Genetic knockdown of *Wnt5a* following initial cancer cell dissemination was sufficient to form overt metastases in young mice, whereas forced overexpression of *Wnt5a* after dissemination prevented overt metastases in previously permissive aged mice, supporting that the aged lung microenvironment shifts cancer cells from high to low WNT5A signaling and promotes the transition from dormancy to reactivation. In addition, reactivation was triggered, in part, through inverse expression of the receptor tyrosine kinases AXL and MER, in which the shift to overt metastatic growth in the lung required low AXL and high MER expression. Together, this work elucidates a mechanism by which a metastatic microenvironment undergoes changes that reawaken dormant cancer cells. ■

Fane ME, Chhabra Y, Alicea GM, Maranto DA, Douglass SM, Webster MR, et al. Stromal changes in the aged lung induce an emergence from melanoma dormancy. Nature 2022;606:396–405.

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