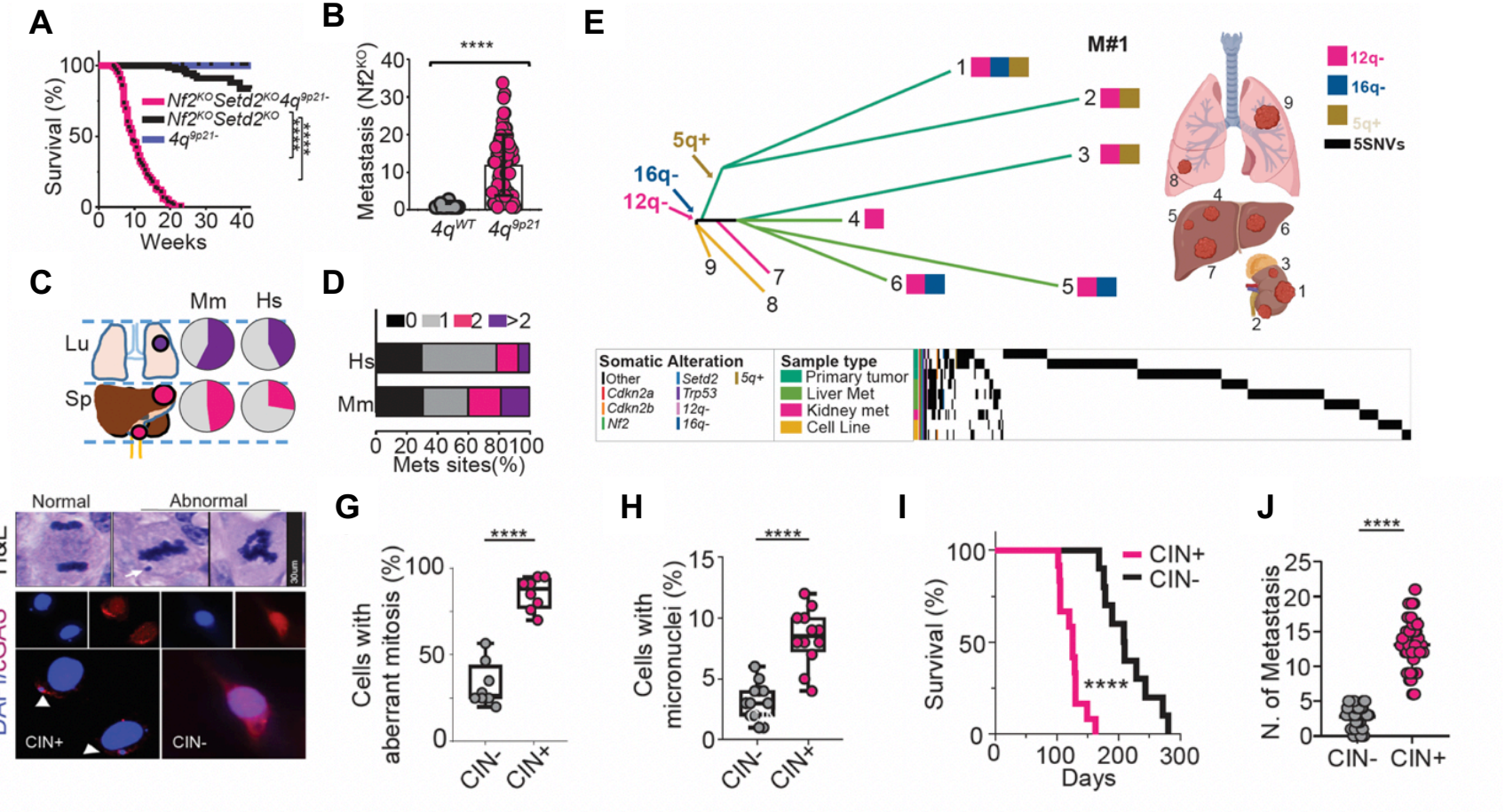
Convergent evolutionary trajectories uncover metastatic drivers in renal cancer

1. Loss of 9p drives metastatic disease in RCC

2. Metastatic RCC are characterized by high CIN and engagement of the cGAS/STING pathway



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
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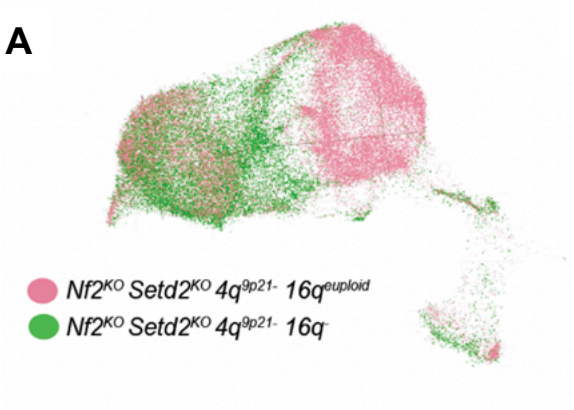
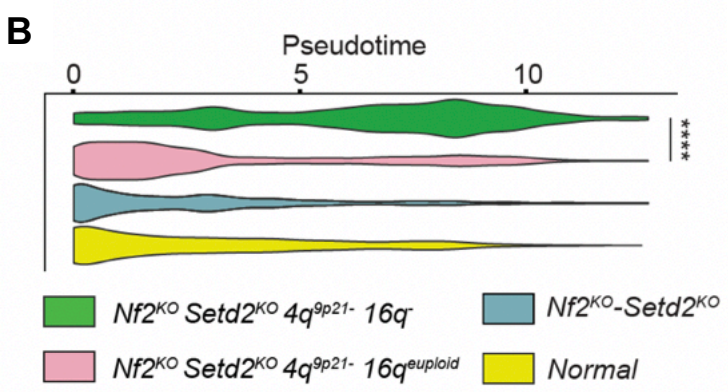
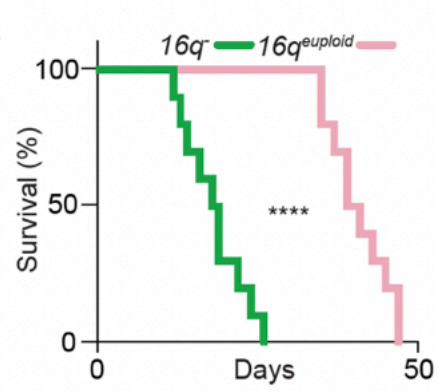
Luigi Perelli, MD, PhD - Genovese Lab, Genitourinary Medical Oncology

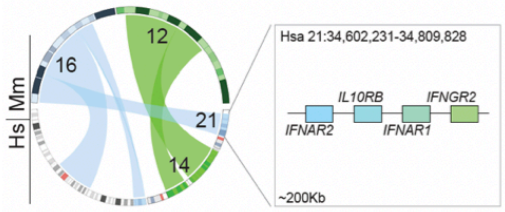
3. Transcriptomic single cell RNA seq & genomic data shows that RCC with loss of 9p mainly differ for the loss of 16q- syntenic to human chromosome 21q

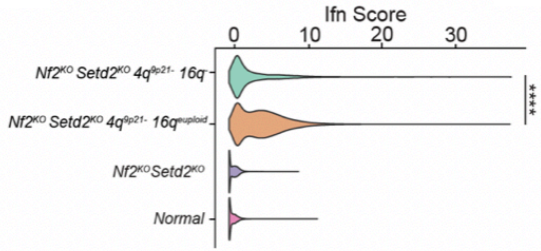
4. Loss of 21q drives down-modulation of the interferon pathway

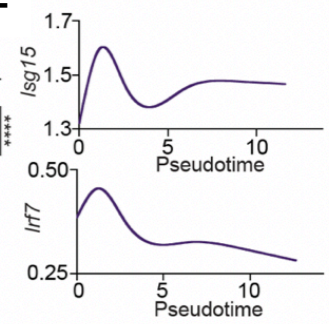


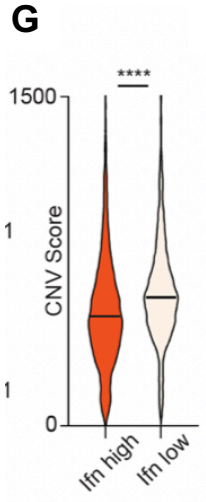


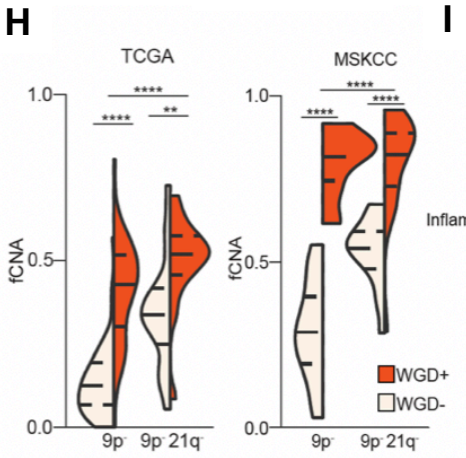


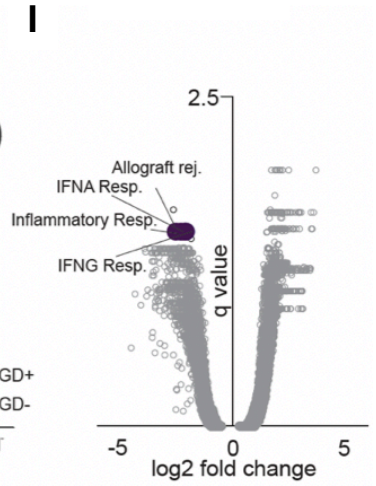


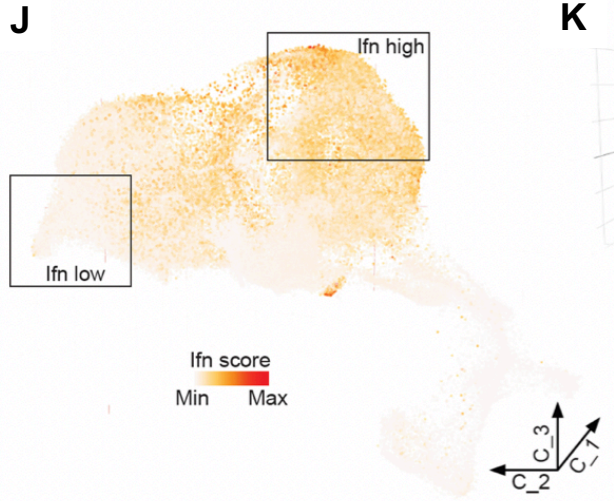


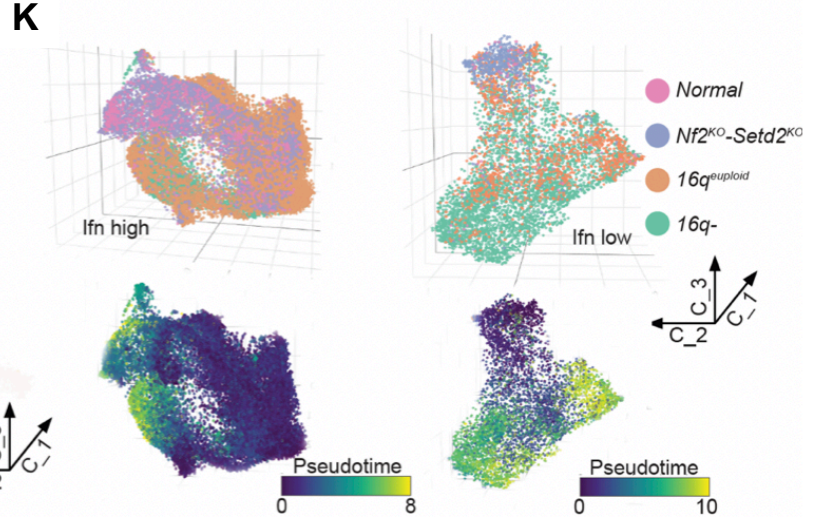


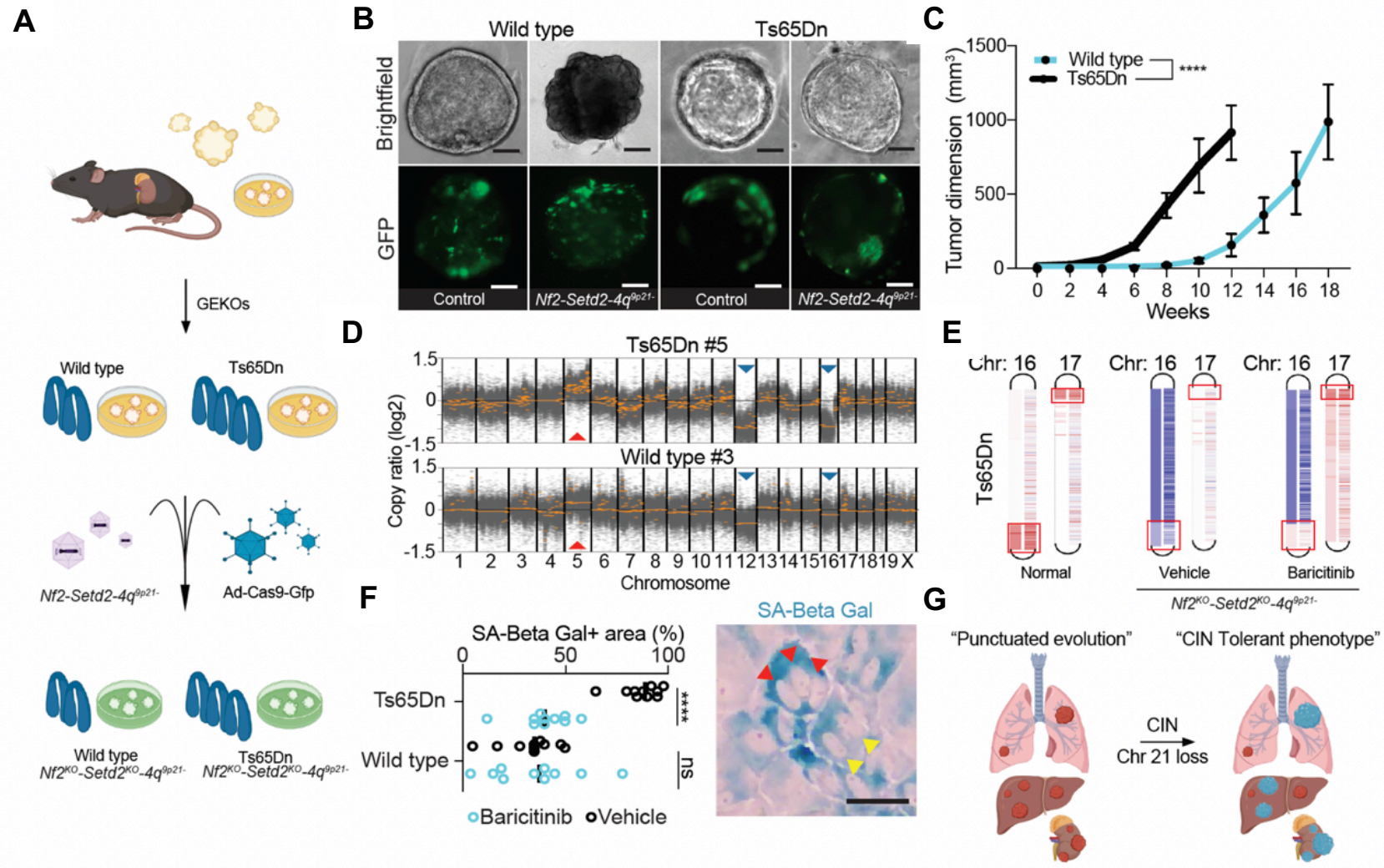












5. Gain of function experiments using a model of Down Syndrome with partial trisomy of chromosome 21 is able to rescue the pro-tumorigenic phenotype induced by 21q loss

6. 21q loss pro-tumorigenic phenotype is driven by suppression of the interferon signaling

Conclusions: our findings indicate that metastatic dissemination of clear-cell and non-clear-cell RCC is driven by CIN, following a model of punctuated equilibrium. We also discovered a tumor suppressive role of chromosome 21q. These findings elucidate molecular drivers of metastatic dissemination in RCC and may provide new biomarkers to intercept and prevent aggressive clinical behavior.