Clonal dissection of pancreatic tumors unmasks functional and genomic heterogeneous long-term self-renewing compartments at the origin of treatment resistance

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Intrinsic and adaptive drug-resistance mechanisms allow human tumors to evade treatment through the demonstrated expansion of treatment-resistant clones. Thus, tumors are complex, dynamic ecosystems wherein populations of cells harboring both founder clones and unique, subclonal mutations coexist and progressively evolve. Modeling this functional heterogeneity of tumors can uncover critical contributions of distinct tumor cell sub-populations toward identifying rational drug combinations. Here, studying clonal evolution of tumor cells derived from human pancreatic tumors, we demonstrate that in vitro adherent cultures and in vivo tumors are maintained by a common set of long-term self-renewing cells that can be used to establish Clonal Replica Tumors (CRTs), large cohorts of animals bearing human tumors with identical clonal composition. Using CRTs to conduct quantitative assessments of clonal dynamics and adaptive responses to therapeutic challenge across different animals over time, we uncovered that the long term self-renewing compartment of pancreatic cancer is represented by a multitude of functionally heterogeneous subpopulations of cells with differential degrees of sensitivity to therapeutics. Consistent with the stem cell hypothesis, although tumors respond to treatments and undergo a transient regression, their clonal complexity at the time of relapse is only partially compromised, implying that many tumorigenic cells survive the treatment and sustain tumor relapse. Moreover, our ability to track the same cell populations in different animals enabled us to demonstrate that the clonal composition of relapsed pancreatic tumors varied across the different drug treatment groups (gemcitabine, MEK1 inhibitor and dual PI3K/mTOR inhibitor), suggesting that the compartment of long-term self-renewing tumorigenic cells is highly functionally diverse in mediating drug resistance to different therapies. Notably, high-throughput isolation and deep characterization of unique clonal lineages isolated through CRTs demonstrated that individual self-renewing populations display a remarkable genetic and molecular heterogeneity that can account for the differential functional responses and adaptation to perturbations. So, our findings portend a model in which the genomic and functional heterogeneity within human tumors is maintained, propagated and recapitulated entirely by distinct pools of long-term self-renewing cells. This concept has important implications for the efficacy of pharmacological combinations, which has historically been ascribed to their synergistic effects to abrogate the emergence of resistance, may instead be linked to the ability of mechanistically unrelated drugs to delay relapse by targeting multiple populations of tumorigenic cells simultaneously.