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Combinatorial CRISPR profiling of driver gene permutations that underlie breast cancer

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Most common human adult cancers involve the alteration of multiple driver genes. Certain features of how driver genes collaborate to promote cancer are known, including their relative timing during cancer progression and their functions in different oncogenic signaling pathways. However, the degree to which cancer results from genetic interactions (epistasis) between driver genes as opposed to the sum of individual driver gene effects is largely unknown. Greater knowledge of epistatic interactions among driver gene alterations is necessary to accurately predict which phenotypes and therapeutic vulnerabilities are to be expected based on a patient's cancer genome. However, uncovering these epistatic interactions and understanding their contribution to cancer progression has not been possible until the development of combinatorial CRISPR profiling that integrates CRISPR phenotypic screening with single-cell transcriptome readouts. We used this methodology to systematically analyze how combinations of inactivated tumor suppressor genes (TSG) changed the growth properties and gene expression profiles of human mammary epithelial cells, with the goal of identifying general mechanisms of driver gene cooperation. We prepared several derivatives of the commonly used nontumorigenic breast epithelial model, MCF10A. Derivatives of MCF10A were infected with a combinatorial CRISPR library targeting 52 TSGs and cultured *in vivo* by injection into murine mammary fat pads. These cells with diverse genotypes then competed with one another for 6 to 8 weeks, allowing for the identification of epistatic interactions, which are the pairwise perturbations that result in faster than expected tumor cell growth. Surprisingly, the epistatic interaction networks were comprised of numerous cliques—sets of three or four genes such that each TSG within the clique showed oncogenic cooperation with all other genes in the clique. Single-cell transcriptomic profiling of CRISPR double knockouts revealed that cooperating TSGs that synergized in promoting tumorigenesis showed transcriptional epistasis, whereas noncooperating TSGs did not. These epistatic transcriptional changes, both buffering and synergistic, affected the expression of oncogenic mediators and therapeutic targets, including CDK4, SRPK1, and DNMT1. Importantly, the epistatic expression alterations caused by dual inactivation of TSGs in this system, such as PTEN and TP53, were also observed in patient tumors, establishing the relevance of these findings to human breast cancer. Overall, our study indicates that transcriptional epistasis is a central aspect of multigenic breast cancer progression and provides a roadmap for moving beyond the discovery and development of therapeutic strategies based on single.

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