A137 · Evolutionarily constrained immunotherapy targets encoded by oncogene amplicons in cancer

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Oncogenic amplifications drive tumor growth and evolution, frequently co-amplifying genes physically adjacent to the driver. These passenger genes are candidates for immunotherapy, but their durability depends on whether they remain physically linked to the driver through evolution. Persistence of linkage is shaped by the architecture of the amplicon, which can take different forms (integrated, breakage-fusion-bridge, or ecDNA) and mitotic segregation patterns. Integrated amplicons are inherited with chromosomal fidelity, whereas extrachromosomal DNA lacks a centromere, segregates randomly, and can be gained or shed within a few divisions.

We hypothesize that this difference in ongoing mutational and segregation processes makes integrated amplicons give rise to more clonally stable therapeutic targets than ecDNA. To address this, we reconstructed and classified focal amplifications using bulk whole genome sequencing across tumors and tumor-derived cell lines from four pan-cancer cohorts (TCGA, PCAWG, Hartwig, CCLE). We build breakpoint graphs to resolve amplicon topology and classify recurrent driver-passenger pairs. We extend this classification by examining structural features, including genomic distance, copy number, and breakpoint position. While increased gene dosage creates more opportunity for transcription, mechanisms including transcriptional silencing, availability of transcriptional machinery, and disruption of regulatory elements at breakpoints undermine the durability of clonally stable candidates. We relate amplicon structural context to matched bulk RNA co-expression to test preservation of regulatory coupling across driver-passenger pairs. Finally, we assess if amplicon architecture predicts viability as a therapeutic target, using structural atlas candidates from tumor-derived cell lines and cross-referencing them with genome-wide CRISPR-Cas9 loss-of-function screens across the DepMap cell-line panel.