Mutations

Major Finding: Driver mutations were identified in cryptic splice regions, 5′ UTRs, and rarely mutated genes.

Approach: Probabilistic deep learning enabled genome-wide modeling of mutation rates in different cancers.

Impact: This work introduces a publicly available resource to identify drivers of cancer genome-wide.

GENOME-WIDE MUTATION RATE MODELING IDENTIFIES NOVEL DRIVER MUTATIONS

Computational methods to discover key drivers of cancer have provided insights into mechanisms of tumor progression and highlighted opportunities for therapeutic intervention. The identification of driver mutations requires distinguishing between somatic mutations that undergo positive selection within tumors and neutral mutations that reflect background mutational processes. Because mutational rates vary widely depending on genomic context, efforts to characterize driver mutations have often been limited to protein-coding sequences and specific noncoding elements. To address these limitations, Sherman, Yaari, Priebe, and colleagues developed a probabilistic deep learning model to identify driver mutations genome-wide by calculating rates of somatic mutations genome-wide in a given type of cancer. Integrating datasets of somatic mutations spanning 37 tumor types from the Pan-Cancer Analysis of Whole Genomes and epigenetic information from healthy tissues, the model predicted rates of mutation based on properties that impact DNA repair and cancer-specific mutational processes. After generating a cancer-specific genome-wide map of mutational rates, the model was used to search for single-nucleotide variants (SNV) with evidence of positive selection and not only exceeded the performance of more limited methods but also required less runtime. At the pan-cancer level, SNVs at intronic cryptic splice sites in tumor suppressor genes such as *TP53* and *SMAD4* occurred significantly more often than expected given mutation baseline rates, whereas conversely oncogenes were not enriched for intronic cryptic splice SNVs, suggesting that positively selected cryptic splice mutations likely cause a loss of function. In addition to cryptic splice sites, the model also identified candidate driver mutations within the 5′ untranslated regions (UTR) of *TP53* and the transcription factor *ELF3*. Notably, the model enabled identification of rare driver genes, demonstrating that the distribution of SNVs in a rare driver of a given cancer mirrored that of a cancer in which it is more common. In summary, this study provides a tool to enhance the understanding of putative drivers of cancer throughout the genome. ■

Sherman MA, Yaari AU, Priebe O, Dietlein F, Loh PR, Berger B. Genome-wide mapping of somatic mutation rates uncovers drivers of cancer. Nat Biotechnol 2022 Jun 20 [Epub ahead of print].

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Immunology

Major Finding: Depleting components of the cBAF chromatin remodeling complex improves antitumor T-cell function.

Concept: Chromatin remodeling complexes cBAF and INO80 enforce the epigenetic state of exhausted CD8$^+$ T cells.

Impact: Targeting ARID1A can enhance CD8$^+$ T-cell persistence and viability, improving immunotherapy outcomes.

CHROMATIN REMODELING FACTORS DRIVE EPIGENETIC CHANGES CRUCIAL FOR T-CELL EXHAUSTION

Chronic T-cell stimulation promotes T-cell exhaustion and reduced immunotherapy efficacy as well as global changes to the transcriptome and epigenome; however, the factors that drive this transformation remain undetermined. By performing a genome-wide CRISPR screen in an *in vitro* model of T-cell exhaustion that recapitulates *in vivo* transformations, Belk and colleagues identified the chromatin remodeling complexes cBAF and INO80 as critical genetic regulators of T-cell exhaustion. An *in vivo* CRISPR screen (limited to the top 300 hits of the *in vitro* genome-wide screen) in two murine models also showed consistent results with perturbations of cBAF and INO80 chromatin remodelers preventing T-cell exhaustion in response to chronic antigen stimulation. Functional assays revealed that blocking T-cell exhaustion by depleting subunits of the cBAF complex improves T-cell antitumor activity *in vivo*, and genetic ablation of the cBAF component *ARID1A* in primary human CD8$^+$ T cells increases viability, persistence, and antitumor activity. In order to understand the molecular mechanism driving improved T-cell function, a limited single-guide RNA pool targeting INO80 and BAF complex components was generated and showed, using Perturb-seq on *in vivo* murine T-cell populations, that cBAF and INO80 complexes were found to have distinct transcriptional roles in T-cell exhaustion. Targeting cBAF subunits *Arid1a*, *Smarcd2*, and *Smarcc1* induced shared gene expression changes, including an increase in effector molecules *Gzmb* and *Ifng* and a global enrichment in T-cell activation programs, while targeting INO80 complex members significantly altered metabolism-related genes. Assay for transposase-accessible chromatin with high-throughput sequencing following ARID1A knockout in both murine and primary human CD8$^+$ T cells further exhibited a global decrease in accessibility of genomic regions unique to chronic stimulation, with the epigenome of these ARID1A knockout cells being more similar to naïve and activated T-cell populations. In summary, this study demonstrates that cBAF and INO80 complexes epigenetically dictate T-cell exhaustion in response to chronic stimulation and suggests improvement can be made to cancer immunotherapies through modulation of this epigenetic state. ■

Belk JA, Yao W, Ly N, Freitas KA, Chen YT, Shi Q, et al. Genome-wide CRISPR screens of T cell exhaustion identify chromatin remodeling factors that limit T cell persistence. Cancer Cell 2022;40:768–86.e7.

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