Lung Cancer

Major finding: Deletion of *Gata2* or inhibition of its targets induces regression of *Kras*-mutant NSCLC.

Mechanism: GATA2 mediates survival through regulation of Rho and IL-1 signaling and the proteasome.

Impact: Inhibition of druggable GATA2 targets may be effective in *KRAS*-mutant lung cancers.

KRAS-MUTANT LUNG CANCERS ARE ADDICTED TO GATA2

KRAS is one of the most commonly mutated genes in non–small cell lung cancer (NSCLC). Previous screens for genes necessary for *KRAS*-mutant NSCLC survival have generally not examined the systemic effects of targeting essential genes or whether inhibiting potential targets can induce regression of established tumors. In an RNAi screen, Kumar and colleagues identified the gene encoding the transcription factor GATA2 as specifically essential to *KRAS*-mutant NSCLC cell line survival both *in vitro* and in tumor xenografts. Simultaneous deletion of *Gata2* and expression of mutant *Kras* in the lungs of mice also led to a significant decrease in the number of tumors formed. Importantly, whole-body deletion of *Gata2* after *Kras*-mutant tumors had already formed was well tolerated and led to tumor regression in 100% of mice. Gene expression analysis following GATA2 knockdown in human NSCLC cells revealed that GATA2 is required for activation of a broad transcriptional network affecting the proteasome complex, interleukin-1 signaling, and the RHO pathway. Reactivation of any of these pathways after GATA2 knockdown partially rescued the viability of *KRAS*-mutant NSCLC cells, suggesting that KRAS-mutant cells are collectively dependent on these members of the GATA2 signaling network. Because transcription factors such as GATA2 are difficult to target with small molecules, the authors therefore tested whether combining clinically available proteasomal and Rho signaling pathway inhibitors would induce regression of established *Kras*-mutant murine lung tumors. Indeed, combined treatment with bortezomib, a proteasome inhibitor, and fasudil, a selective Rho pathway inhibitor, led to significant reductions in tumor burden, number, and size compared with either drug alone. This study thus identifies a form of nononcogene addiction in *KRAS*-mutant NSCLC and indicates that combined inhibition of GATA2 targets with clinically available small-molecule inhibitors may be an effective therapeutic strategy in these tumors. ■

Kumar MS, Hancock DC, Molina-Arcas M, Steckel M, East P, Diefenbacher M, et al. The GATA2 transcriptional network is requisite for RAS oncogene-driven non–small cell lung cancer. Cell 2012;149:642–55.

Sequencing

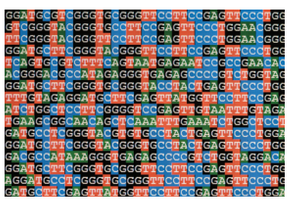
Major finding: Commercially available benchtop sequencers differ in accuracy, throughput, and read length.

Approach: The same *E. coli* isolate was sequenced with 3 different benchtop high-throughput sequencers.

Impact: An unbiased performance, time, and cost comparison can inform laboratory purchasing decisions.

BENCHTOP SEQUENCING INSTRUMENTS ARE COMPARED HEAD-TO-HEAD

DNA sequencing technology has advanced and equipment costs have decreased to the point where benchtop instruments are now available and affordable for many clinical and research laboratories. Loman and colleagues report the results of a performance comparison between 3 commercially available benchtop high-throughput sequencing instruments: the Roche 454 GS Junior, the Illumina MiSeq, and the Life Technologies Ion Torrent Personal Genome Machine (PGM). The authors used each instrument to sequence an *Escherichia coli* isolate and calculated a quality score for each sequencer by aligning reads to a reference genome and identifying nucleotide substitutions, insertions, and deletions independently of the manufacturer's analysis software. Notably, there was a high degree of variation in the number, length, accuracy, and genome coverage of reads produced by the 3 sequencers. The MiSeq, the only instrument that does not require manual preparation of amplified sequence libraries, produced a much higher number of reads and had significantly



fewer errors than the 454 GS Junior or the Ion Torrent PGM. However, the MiSeq is the most expensive of the instruments and had the longest run time. The least expensive instrument, the Ion Torrent PGM, also had the shortest read time, but produced short reads with the most errors and gaps and covered the least of the reference genome. The 454 GS Junior obtained the longest reads, but had a much lower total number of reads than the other machines, resulting in the highest cost per megabase sequenced. This unbiased analysis, which reveals advantages and disadvantages of each sequencer, may be informative to those considering benchtop high-throughput sequencing instruments for their laboratories. ■

Loman NJ, Misra RV, Dallman TJ, Constantinidou C, Gharbia SE, Wain J, et al. Performance comparison of benchtop high-throughput sequencing platforms. Nat Biotechnol 2012;30:434–9.

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