CANCER

A trio of new mice for studying *KRAS* biologyZafra, M.P. et al. *Canc Discov* (2020) <https://doi.org/10.1158/2159-8290.CD-20-0442>

When talking about cancer research, *KRAS* is bound to come up. The oncogene is one of the most frequently mutated in human cancers, but not all *KRAS* mutations are alike. As researchers and clinicians have sequenced more and more individual tumors from patients, it has become clear that there's more to the story than whether or not the gene is mutated.

"People have started to look at these databases and are starting to realize, well, you get a mutation in the *KRAS* gene – that is not always the same mutation," says Maria Paz Zafra, a postdoctoral fellow in Lukas Dow's lab at Weill Cornell Medicine in New York. From organ to organ, biases appear – a particular *KRAS* variant will be prevalent in say, colon cancers, but less commonly found in pancreatic or lung cancers. The available animal models to test the consequences of such differences, however, were limited. It was time to make some more mice.

With the help of CRISPR-Cas9, Zafra and her colleagues add three conditional

mutant *KRAS* models to the cancer field's mouse cache: *KRAS*^{G12C}, *KRAS*^{G12R}, and *KRAS*^{G13D}. The chosen allelic variants, subtly different and found quite close together on codons 12 and 13, are common in lung, pancreatic, and colon cancers, respectively. When the team induced the different alleles *in vivo* in mouse colon and pancreas epithelial tissue, they noted tissue-specific differences in tumor initiation and early development; additional work with pancreatic organoids revealed differences in drug sensitivities depending on the particular mutation as well.

Developing the appropriate strategy to make the mice took two long years, says Zafra. Despite its oncogenic potential, *KRAS* is essential for normal embryonic development so it can't be mutated too early; Cas9, meanwhile, can be promiscuous and cut unintended locations, and the team found themselves working through a number of guides and Cas9 variants to find the one that would only edit the conditional allele in their embryonic cell

lines while leaving the wild-type copy untouched. To save others the same trouble, the team has deposited two of the three mouse models in the Jackson Laboratory's repository, with the third to follow soon, Zafra says.

Although the new mice can help add nuance to preclinical work exploring the oncogene's influences on cancer, that's still the easy part, says Zafra. *KRAS* doesn't operate alone – there are now additional co-mutations in other genes to start considering, and more tumor-specific context to explore. Nevertheless, she hopes the field will find the conditional mouse models a valuable addition. "They reflect this variability that we get across human tumors," she says. "It will definitely help us keep studying *KRAS* biology, but in a very specific manner."

Ellen P. Neff

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