RAS mutation tropism

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Oncogenic mutations in HRAS, NRAS and KRAS commonly occur in a wide spectrum of human cancers. These mutations are not uniform but instead have a tropism, namely the frequency, RAS isoform, position and type of mutation are often unique to each cancer. There is no definitive mechanism to explain this clinical finding, although the pattern itself has been widely reported for decades. As oncogenic RAS can induce tumorigenesis, the mutation tropism of these genes must underlie some fundamental feature of tumor initiation, or to put it another way, how cancer arises. Determining how specific RAS mutations occur would thus shed light on the process of cancer initiation, which has clinical implications for early detection and perhaps even preventative measures. This phenomenon is recapitulated in mice exposed to the environmental carcinogen urethane, which develop KrasQ61L/R-mutant pulmonary tumors, making urethane carcinogenesis an ideal platform to elucidate the underlying principles of RAS mutation tropism. To this end, we adapted the error-corrected, high-throughput sequencing approach of maximum depth sequencing to detect mutations in the endogenous murine Kras gene at great sensitivity in vivo, capturing the initiating mutations following urethane exposure. Further, by sequencing Kras as well as Hras in this manner and from different tissues and over time, we find that the sequence specificity of urethane mutagenesis, coupled with Kras transcription, to be major influences on the extreme tropism of this carcinogen.

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