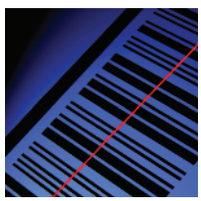
DNA Repair

Major finding: 53BP1 accumulates at double-strand breaks upon recognition of H4K20me2 and H2AK15Ub.

Concept: 53BP1 is a site-specific histone ubiquitination reader with selectivity for H2AK15Ub.

Impact: The response to DNA double-strand breaks involves the detection of a histone code.

53BP1 BINDS DNA DAMAGE–INDUCED H2AK15UB



Following DNA double-strand breaks (DSB), multiple proteins are recruited to chromatin in a sequential manner to mediate various aspects of the DNA damage response. 53BP1 is a chromatin-binding protein that is recruited to DSBs to promote DNA repair by nonhomologous end joining. 53BP1 binding to chromatin is mediated by its tandem Tudor domain, which recognizes dimethylated histone H4 lysine 20 (H4K20me2). However, because 53BP1 recruitment to DSBs also requires the E3 ubiquitin ligase RNF168, exactly how ubiquitin promotes the accumulation of a methyl-histone binding protein at break sites remains a mystery. To better understand the ubiquitin-dependent mechanism of 53BP1 recruitment to DSBs, Fradet-Turcotte and colleagues turned to the *Schizosaccharomyces pombe* 53BP1 ortholog, Crb2. Like human 53BP1, Crb2 has a tandem Tudor domain that binds H4K20me2, but fission yeast do not have a RNF168 homolog, and Crb2 does not form DNA damage-induced foci when expressed in human cells. Mapping of the regions of human 53BP1 that could restore foci formation when fused to Crb2 identified a region C-terminal to the Tudor domain the authors termed the ubiquitin-dependent recruitment (UDR) motif. The UDR was required for 53BP1 accumulation at DSBs as well as for its downstream roles in the DNA damage response, and specifically interacted with ubiquitinated histone H2A within polynucleosomes. 53BP1 binding was specific to monomeric nucleosome core particles containing H4K20me2 and ubiquitinated histone H2A lysine 15 (H2AK15Ub). Given that RNF168 can also ubiquitinate H2AK13Ub, this finding suggests that other ubiquitin marks on histones may have their own sets of readers, thus expanding the repertoire of instructive histone marks. The identification of 53BP1 as a bivalent reader of H4K20me2 and H2AK15Ub therefore explains how ubiquitination recruits 53BP1 to DSBs and illustrates the importance of distinct histone modifications in orchestrating the DNA damage response. ■

Fradet-Turcotte A, Canny MD, Escribano-Díaz C, Orthwein A, Leung CC, Huang H, et al. 53BP1 is a reader of the DNA damage-induced H2A Lys15 ubiquitin mark. Nature 2013;499:50–4.

Genomics

Major finding: Incorporating mutational heterogeneity into genomic analyses may reveal the most likely driver genes.

Concept: Failing to correct for patient-specific and gene-specific mutation rates generates false positives.

Impact: The long lists of significantly mutated genes in large cancer genome studies may be artifactual.

CANCER GENOMIC STUDIES MAY BE CONFOUNDED BY MUTATIONAL HETEROGENEITY

A major impetus for the initiation of large cancer sequencing projects has been the idea that large sample sizes will increase the power to identify genes mutated above the background mutation rate. However, as cancer genome study sample sizes have increased, the lists of significantly mutated genes have also grown. Lawrence and colleagues noted that these lists commonly include implausible candidate genes based on known biologic functions and are highly enriched for genes with specific genomic features, such as extremely long coding regions or introns. The authors hypothesized that current analytic methods identify so many specious genes because they fail to account for mutational heterogeneity that affects the background mutation rate. Using whole-exome or whole-genome sequencing data from over 3,000 matched tumor–normal pairs representing 27 different cancer types, they found that the mutation frequency varied by several orders of magnitude across patients with a given cancer type. This finding indicates that the assumption that cancers of a given type have a constant mutation rate is erroneous and could affect the accuracy of results. Another issue was that although individual tumor types tended to share a similar mutational spectrum, variability among individual samples suggested that current models of mutational processes used to calculate the background mutation frequency could be too simplistic. Finally, regional mutational heterogeneity appeared to be a key underlying cause of the identification of some suspect genes, as somatic mutation frequency was strongly correlated with low gene expression and late DNA replication. Taking these issues into account, the authors developed a method that would correct for patient- and gene-specific mutational heterogeneity and be capable of identifying much shorter lists of plausible significantly mutated genes. Accounting for mutational heterogeneity may therefore eliminate artifactual results in cancer genome studies and facilitate the identification and further validation of true cancer-associated genes. ■

Lawrence MS, Stojanov P, Polak P, Kryukov GV, Cibulskis K, Sivachenko A, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature 2013;499:214–8.