p53: out of Africa

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Somatic mutations in the tumor suppressor gene p53 occur in more than half of all human cancers. Rare germline mutations result in the Li-Fraumeni cancer family syndrome. In this issue of *Genes & Development*, Jennis and colleagues (pp. 918–930) use an elegant mouse model to examine the affect of a polymorphism, P47S (rs1800371), in the N terminus of p53 that is found in Africans as well as more than a million African Americans. Remarkably, the single nucleotide change causes the mice to be substantially tumor-prone compared with littermates, suggesting that this allele causes an increased risk of developing cancer. The defect in p53 function is traced to a restriction in downstream gene regulation that reduces cell death in response to stress.

Li-Fraumeni syndrome, which is caused by germline mutations in the p53 gene, has been extensively studied. It is associated with an extraordinarily high risk of cancer development of various types, including pediatric sarcomas and brain cancers as well as very early onset female breast cancer (Malkin et al. 1992). The severity of the syndrome is related to the exact nature of the mutation in p53, with missense mutations in the DNA-binding domain predominating. Interestingly, a large cohort of individuals in Brazil that harbor a mutation in the C terminus of p53 show a much milder phenotype, generally presenting with adrenocortical tumors as young adults. Mouse models of Li-Fraumeni syndrome reflect these features. Using the hybrid mouse/human Hupki allele of p53 (Luo et al. 2001), a range of p53 point mutations has been tested for their effects on tumor incidence and spectrum in mice. Broadly, the results show that missense mutations in p53 result in higher tumor incidence in mice, although the type of tumors that develop is strongly dependent on strain background. This finding emphasizes the importance of modifier genes in the mechanisms of p53 tumor suppression (Goh et al. 2011). Indeed, polymorphic variations in the promoter of Mdm2, a p53 target gene and negative regulator, show effects on tumor incidence in both mouse models and Li-Fraumeni cohorts, thereby defining it as a modifier gene (Pietsch et al. 2006; Grochola et al. 2010).

Further analysis suggests a difference between p53 alleles based on the exact nature of the mutation. For example, some alleles show a dominant-negative phenotype, while others also show a gain of function. In these cases, the mutant protein induces phenotypes like invasion and metastasis that differ from the effects of simple loss of function (Muller and Vousden 2014). These findings, along with clear cell biological studies that demonstrate that p53 is cell-autonomous and haploinsufficient for cell death responses to radiation, suggest that the precise level and biochemical nature of the p53 protein can profoundly modify its tumor suppressor activity. The potential significance of known p53 polymorphisms in the human population is thus a matter of great interest, as these variations in p53 may affect an individual's risk of developing cancer. Murphy's team (Jennis et al. 2016) has recently examined two such polymorphisms. The first, a variant P or R at amino acid 72, seems to affect metabolism. When introduced into the HIPKI mice, the R allele results in a higher rate of obesity in animals fed a high-fat diet. Interestingly, this allele is more prevalent in human populations found in colder climates distant from the equator. However, R allele variations have not been linked to increased human cancer incidence, and the mice were not reported to show any allele-specific excess risk (Kung et al. 2016). Therefore, the current study is especially provocative because it demonstrates a dramatic increase in cancer development in the majority (16 out of 20) of S47 homozygous animals between 12 and 18 mo of age. The tumors were also highly unusual compared with the reported phenotypes of other p53 mutant mice. The S47 mice generally develop hepatocellular carcinoma (HCC; six out of 13 tumor-positive mice), while, in either p53-null mice or those with mutations in the p53 DNA-binding domain, thymomas and sarcomas are the dominant tumor types. The wild-type littermate controls developed no tumor in the observation period. Even more striking is the finding that four out of six tumor-bearing heterozygote mice also showed the development of HCC. The effect of the S47 allele is thus genetically dominant, and it will certainly be important to assess whether these HCC tumors have lost the wild-type p53 allele.

How does the single amino acid change (resulting from a single base change, G/A) in the whole genome have such a profound effect, and why is the phenotype so different from that seen in p53-null mice? The properties of the S47 mutant p53 protein come in for close scrutiny, as does the nature of the p53 response in both mouse and human cells that express the S47 protein. At the cellular level, the investigators can test not only cells derived from their new mice but also human lymphoblastoid cell lines derived from homozygous S47 or P47 donors. The cells show a clear but very selective defect in the cell death response to the commonly used anti-cancer drugs cisplatin, CDDP, and adriamycin; however, the response to ionizing radiation is not affected by the polymorphism. Tracking this down further by examining patterns of gene expression suggests that the S47 p53 protein is defective in its activation of a small subset of p53 target genes, including Gls2, Noxa, and Sco2. Mechanistically, this correlates to a lack of p53 binding to response elements of these selective genes when analyzed by chromatin immunoprecipitation. This must mean that some modification of p53 itself that affects p53 DNA-binding specificity either directly or by recruiting a partner protein is absent in the S47 protein. A compelling candidate for this modification is the phosphorylation of S46 of p53, as the S46 kinases are unable to phosphorylate S47 p53 but can phosphorylate the wild-type P47 protein. Finally, as Gls2 has been reported to affect a new form of cell death, the investigators confirm that the S47 cells are resistant to the ferroptosis (Jiang et al. 2015) that is induced by the drug RSL3.

The results need to be extended to larger cohorts of mice, and the allele should be tested on different strain backgrounds in the future. As the S47 allele occurs only in cis with the P72 variant of p53, the mice were made on this background. It would be fascinating to see whether the combination of the S47 and R72 variants of p53 is embryonically lethal.

The most profound implications, though, are for the African and African American individuals that bear the S47 allele. There are an estimated 20,000 S47 homozygotes and 1 million S47 heterozygotes in the United States alone and many more in Africa. Are these individuals at increased risk of developing cancer and, if so, would they benefit preferentially from a focused screening program? Does the organ specificity seen in the mice for HCC also occur in humans? Are these individuals less likely to benefit from CCDP therapy of their wild-type p53 tumors but conversely more tolerant of side effects when the drug is used to treat their p53 mutant cancers? Jennis et al. (2016) have certainly opened a whole new chapter in the story of p53 and its impact on human cancer.

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