Drug Response

Major finding: *TSC1*-mutant bladder cancers had better responses to everolimus than *TSC1*–wild-type tumors.

Clinical relevance: Sequencing the tumor genomes of outlier patients may uncover the basis of their drug response.

Impact: mTOR-targeted therapies may be especially effective in patients with somatic *TSC1* mutations.

TSC1 MUTATIONS CONFER SENSITIVITY TO EVEROLIMUS

Even if an anticancer drug has significant activity in a small number of patients, it will be considered inactive and not developed further if most patients experience disease progression or if the median progression-free survival does not increase. Iyer and colleagues reasoned that the tumor genomes of outlier patients who responded to a "failed" drug might provide insight into drug sensitivity and guide patient selection for future trials. A recent phase II trial of the mTOR inhibitor everolimus in metastatic bladder cancer failed to achieve its endpoint of prolonging progression-free survival, but 1 patient who was enrolled in the trial experienced a durable and ongoing complete response lasting more than 2 years. The authors performed whole-genome sequencing of this patient's primary tumor and identified a somatic frameshift truncation mutation in *tuberous sclerosis complex 1* (*TSC1*), which encodes a negative regulator of the mTOR pathway. Exon sequencing of 13 additional tumors from patients enrolled in the same trial revealed that 4 other tumors harbored *TSC1* mutations. Of these patients with *TSC1*-mutant tumors, 3 experienced minor responses to everolimus therapy, whereas 8 of the 9 patients in this group that showed disease progression had *TSC1*–wild-type tumors. Furthermore, patients with *TSC1*-mutant tumors remained on everolimus significantly longer than patients with *TSC1*–wild-type tumors and had a significant improvement in time to recurrence. Although limited to a small group of patients, this approach demonstrates the feasibility of identifying biomarkers of drug sensitivity by sequencing the tumor genomes of responders and suggests an approach for the future clinical development of everolimus in a selected patient population. ■

Iyer G, Hanrahan AJ, Milowsky MI, Al-Ahmadie H, Scott SN, Janakiraman M, et al. Genome sequencing identifies a basis for everolimus sensitivity. Science 2012 Aug 23 [Epub ahead of print].

Neuroblastoma

Major finding: Common SNPs within *HACE1* and *LIN28B* are linked to neuroblastoma susceptibility.

Clinical relevance: Low *HACE1* expression and high *LIN28B* expression are associated with worse overall survival.

Impact: These risk alleles may promote neuroblastoma via decreased HACE1 and increased LIN28B activity.

HACE1 AND *LIN28B* VARIANTS ARE ASSOCIATED WITH NEUROBLASTOMA

Familial neuroblastoma predisposition genes have recently been identified, but the genetic basis of sporadic cases, which account for 99% of neuroblastomas, remains less understood. Common variants within several genes have previously been linked to neuroblastoma but only explain a small portion of disease susceptibility. To identify additional genomic variants associated with neuroblastoma risk, Diskin and colleagues performed a genome-wide association study in over 2,000 neuroblastomas and 4,000 controls, and found 2 single-nucleotide polymorphisms (SNP) on chromosome 6q16 that reached genome-wide significance. Further analysis of this region uncovered association signals implicating 2 genes—*HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1* (*HACE1*) and *lin-28 homolog B* (*LIN28B*)—that were also identified in 2 independent validation cohorts. Notably, *HACE1* downregulation has been observed in multiple human cancers, and *Hace1*-null mice are tumor prone, suggesting that risk alleles in *HACE1* may affect its tumor suppressor activity. Conversely, *LIN28B* risk alleles may promote LIN28B oncogenic activity, as several human cancers express high levels of *LIN28B* and ectopic *LIN28B* overexpression induces cellular transformation. Consistent with this possibility, neuroblastoma cell lines that were homozygous for the *LIN28B* risk allele had significantly higher *LIN28B* expression, although no correlation between the *HACE1* SNP and *HACE1* expression was observed. Furthermore, *LIN28B* knockdown selectively inhibited the growth of neuroblastoma cells homozygous for the *LIN28B* risk allele. In primary tumors, *LIN28B* expression was significantly higher and *HACE1* expression was significantly lower in high-risk tumors than in low-risk tumors, and high *LIN28B* expression and low *HACE1* expression were associated with shorter overall survival. Although further functional studies are needed, these findings suggest that common variants affecting HACE1 and LIN28B function may contribute to neuroblastoma susceptibility. ■

Diskin SJ, Capasso M, Schnepp RW, Cole KA, Attiyeh EF, Hou C, et al. Common variation at 6q16 within HACE1 and LIN28B influences susceptibility to neuroblastoma. Nat Genet 2012 Sept 2 [Epub ahead of print].

Note: *Research Watch* is written by *Cancer Discovery* Science Writers. Readers are encouraged to consult the original articles for full details. For more Research Watch, visit *Cancer Discovery* online at http://CDnews.aacrjournals.org.