Seeing the Forest for the Trees: Kidney Oncogenomes Relate to Therapeutic Outcomes

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Renal cell carcinoma is a heterogeneous disease, and tissue investigations provide clues that may predict treatment response. Oncogenomic analysis of five outliers, who achieved a sustained response with rapalogs, implicates alterations of the TSC1 and mTOR genes and reveals insights into the conserved evolution of tumors. Clin Cancer Res; 20(7); 1–3. ©2014 AACR.

In this issue of Clinical Cancer Research, Voss and colleagues (1) present an impressive and comprehensive analysis of 5 patients whom they observed to be outliers in achieving sustained response to rapalog therapy beyond the typically expected duration of benefit. Using advanced sequencing and bioinformatics tools, to explore the tumor genome of these patients from available specimens, they identified likely mutational events in 3 of the 5 cases that could reasonably account for the unique sensitivity of these patients to treatment with a rapalog.

All of the cases with identified mutations were clear cell renal cell carcinomas (RCC). This disease, recently and extensively characterized by The Cancer Genome Atlas (TCGA), displays mutations in members of the same pathway in a nonredundant fashion in nearly 15% of cases (2). As in this case series, 9p deletion was a common copy-number alteration (2), and as has been previously reported, is associated with higher risk disease (3). Common genes affected by mutation included inactivating mutations in PTEN, TSC1, and TSC2, and mutations in mTOR (which occurred in nearly 6% of all cases; ref. 2). Collectively, genomic alterations in known components of this pathway can be identified in up to 28% of cases. Where the TCGA was unable to assign function to many of these alterations, Voss and colleagues did confirm the pathway activation that would be predicted to result in sensitivity to mTOR inhibitors. In the case of TSC1 mutations identified in patients 1 and 2, the sequence change was clearly that of a loss-of-function allele, and loss of heterozygosity on chromosome 9 was confirmed. For patient 3, who harbored a missense mutation in the kinase domain of mTOR, both in silico and in vitro analysis of this amino acid substitution were performed, revealing a novel hyperactivated allele, which retained sensitivity to rapamycin. This level of validation confirms that this mutation, and possibly others identified in patients, confers some advantage in mTOR signaling.

One of the most striking and interesting findings of this report is the concordance across the disease of each patient of mTOR pathway–activating mutations (Fig. 1). In the three cases with identified genomic events, subsequently tested regions of the tumor or associated metastasis also had mutations that could independently account for the pathway sensitivity. This is particularly important in light of the recent reports that oncogenomic heterogeneity is higher than expected (4), and reactionary anxiety in the field that RCC may be so heterogeneous as to discredit almost any finding that is reported from a single tissue sample. Like all our patients, every one of these cases had a unique story to tell in their mTOR pathway analysis. Patient 1 had three regions sampled from the primary tumor, two with identical TSC1 mutations, and one region with an independent TSC1 mutation, suggesting a convergent (and by definition “later”) event in the evolution of this tumor, similar to patterns reported previously (4). Patient 2, however, had three samples from the primary tumor as well as a metastasis sample, and all of these shared the same TSC1 frameshift and copy-number alteration, suggesting a high level of clonality for this event, as a likely “early” event evolutionarily. Patient 3 had four samples from the primary tumor assessed, two of which contained the studied mTOR mutation, and no focal copy-number alterations, but two other sites sharing a TSC1 mutation, along with the 9p copy-number alteration corresponding for loss of heterozygosity.

In this tumor, does this represent some early branch point for the mTOR-mutated clone, and a separate acquisition of the two events needed at the TSC locus? The number of samples examined is too small to draw any serious conclusion, but it is intriguing that consistent but parallel patterns of mutations could coexist in one patient’s disease, allowing one to speculate that some selective pressure forces these tumors to enhance signaling through this pathway genetically.

But, what about the 2 patients for whom the best analysis that Memorial Sloan-Kettering Cancer Center had to offer...
failed to provide any explanation for their extraordinary response to therapy? The number of samples examined for these cases is limited, and as the authors discuss, DNA sequence offers only one element in conferring tumor phenotype and pathway behavior. Oftentimes, protein-measured outputs provide the final determinant of an activated pathway, and it is unfortunate that patients 4 and 5 were not examined for evidence of pathway activation by phosphoS6, which might have pointed in those cases to unrecognized epigenetic, microRNA, or other sources of drug sensitivity. However, attempts to classify patients on the basis of immunohistochemical stains for phosphoS6 or p70S6kinase or other markers of mTOR pathway activation have not proved so far to provide robust discriminating power in selecting patients who may benefit most from mTOR inhibitor therapy (5). Hence, here too, we lack the tools necessary to determine what aspect or degree of mTOR pathway activation is needed to allow efficacy from mTOR inhibition (6).

So, the mystery remains for some patients, and the state of modern medicine remains imperfect for advising our patients in some cases. These cases give us pause, as it would have been disastrous for both of these patients, with treatment durations reported at 28 and 45+ months, had their doctors advised that they should not receive an mTOR inhibitor on the basis of lacking a recognized pathway-specific mutation. Thus, it only makes sense that these small case series be considered for what they are, and that changes in policies about therapy administration or coverage on the basis of biologic features be made only with considered reflection and analysis of objective data.

Voss and colleagues (1) present several interesting questions relevant for both translational research and patient care. First, is there a selective pressure coming from the “trunk” or early clonal tumor genomic profile of the tumor, or from some unknown pressure of the host or tumor microenvironment (akin to the natural pressures of sunlight, wind, or soil that will force a tree to adopt a particular shape or position)? These studies are a step in the right direction, but cannot begin to answer that question. Only much more extensive analysis of tumors, including perhaps futuristic tools to take more comprehensive snapshots of the whole disease, can address these questions. This selection strategy does not inform us of the incidence of patients with typical or poor response who also harbor mutations. What is the future for advising patients about the merits of mTOR inhibitors or other targeted therapies? Certainly, a host of clinical trials have emerged to try to answer this question. The results of the RECORD-3 study (7) demonstrate that for the general population, the VEGF receptor (VEGFR) inhibitor sunitinib is superior to everolimus in the first-line setting. However, this and other studies that compare mTOR and VEGFR inhibitors (8) do not preclude the possibility that for a subset of patients, mTOR inhibitors may be advantageous. Does it matter if we take a sample from the trunk or the branches? This study would suggest that even that snapshot gives a fair representation of the tumor oncogenome, and is a step in the right direction to identify tools for patient stratification, to ultimately provide our patients personalized cancer care with treatments tailored to the genomics of their tumor.
Disclosure of Potential Conflicts of Interest

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