mTOR Inhibitors in Cancer: What Can We Learn from Exceptional Responses?#

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mTOR Inhibitors in Cancer: What Can We Learn from Exceptional Responses?☆

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several cancer types. Second, we predict that cancers with activating mutations in RHEB, or inactivating mutations in DEPDC5, NPRL2, and NPRL3, will show similar strong response to rapalogs. Third, it is already clear that not all cancers with mutations in members of this pathway will show such extraordinary responses (Iyer et al., 2012). Indeed, there is likely to be a range of responses to rapalogs even for tumors with activating mutations in the mTOR pathway. There are likely several explanations for this phenomenon, including as yet unidentified secondary modifier mutations, the tumor cell genetic and epigenetic states, as well as the possibility that some apparent mutations represent background noise or are subclonal, and did not contribute substantially to tumor development. Fourth, it also apparent that not all rapalog responders have mutations in components of this pathway (Voss et al., 2014). Apart from the mundane possibility that mutations were missed, there is the more important possibility that alternative mechanisms contribute to response, including epigenetic silencing events affecting one or more of the genes encoding proteins that inhibit mTORC1 activation.

Nevertheless, studies of extraordinary responses to rapalogs suggest that routine screening of cancer patients for alterations in the mTOR pathway may be helpful to identify a subset of patients who are much more likely to respond to mTOR-pathway targeted therapies than other patients. The collective prevalence of mTOR pathway mutations is appreciable among the common cancers (2.8% on average), including many cancers in which rapalogs are rarely used (e.g. lung adenocarcinoma, lung squamous cell carcinoma, melanoma, pancreatic adenocarcinoma, uterine carcinoma all have a prevalence >1%) — highlighting the possibility of additional groups of patients who might benefit from these drugs. These observations have now spawned the so-called "basket" trials, clinical trials that enroll patients based on specific mutations rather than tumor types (e.g. NCT02201212, clinicaltrials.gov). Results of these trials should help to elucidate the factors that determine exquisite dependency on the mTOR pathway as well as the principles of extraordinary responses in general.

One challenge of rapalog basket trials is that the list of cancer genes and mutations that lead to sensitivity to mTOR inhibitors is incomplete and still evolving. Ideally, genomically-driven basket trials would have flexible entry criteria, permitting the range of genes and mutations to be dynamically modified during the trial, to take advantage of improved understanding as well as trial experience. In parallel, more detailed characterization of the functional effects of potential activating mutations in mTOR and RHEB (Grabiner et al., 2014) would be valuable in refining entry criteria for rapalog trials.

There is enormous diversity in the clinical response of patients to anti-cancer drugs and in most cases we do not understand why. Many agents in clinical trials “fail” and may be abandoned, yet, as with rapalogs, there are often a few patients in whom these agents have profound activity. Studies of exceptional responses demonstrate that genomic characterization of even a few patients with extraordinary responses can yield important insights. These studies could help us develop methods for matching patients to drugs, highlight effective uses for otherwise “failed” therapies, and design new therapeutic strategies. Findings from these studies may also help us understand mechanisms of therapeutic resistance when it emerges, and may help develop strategies to overcome such resistance (Wagle et al., 2014a). Unlike other large-scale cancer genomics efforts, identifying and characterizing the tumors from even a few extraordinary responses can lead to major insight and advances in cancer therapy.

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Competing Financial Interests

The authors declare that they have no competing financial interests. DJK is a consultant to Novartis. NW is a consultant and stockholder in Foundation Medicine.
References


