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GENETICS

Finding the path to everolimus sensitivity

Bladder cancer is the fourth most common cancer and approximately 5,000 patients die from it each year in the UK alone. The lack of development of new therapeutic agents might partly account for the slow decrease of mortality rates in bladder cancer (5% over the past 15 years) but, in addition, this disease has the highest recurrence rate of all cancers and most patients suffering from it (50–70%) experience either recurrence or disease progression.

David Solit, Gopa Iyer and collaborators were intrigued by the results of a phase II clinical trial assessing the inhibitor of mTOR, everolimus, as a single agent in the treatment of progressive, metastatic bladder cancer, in which one patient showed a complete response to the drug within 1 year of treatment initiation. "We hypothesized that a specific genetic lesion within this patient's tumour was responsible for this dramatic response," explains Iyer.

To test their hypothesis the researchers used whole-genome sequencing of DNA derived from both tumour and peripheral blood from this patient. Of the 17,136 somatic mutations detected, they found a two base-pair deletion in *TSC1*, a gene already found to be mutated in bladder cancer in previous studies. Knockdown of *TSC1* in bladder cancer cell lines resulted in enhanced sensitivity to mTOR inhibition.

The researchers sought to analyse tumours from more patients in the phase II everolimus study. "We found that four patients with minor treatment responses harboured *TSC1* alterations, whereas eight of nine patients with tumour progression harboured wild-type *TSC1*. Patients with *TSC1* mutant tumours had a significant improvement in time to disease recurrence (4.1 versus 1.8 months)."

These results underline the importance of identifying the molecular profile of tumours, so patients can benefit the most from the available targeted therapies.

M. Teresa Villanueva

Original article Iyer, G. *et al.* Genome sequencing identifies a basis for everolimus sensitivity. *Science* doi:10.1126/science.1226344