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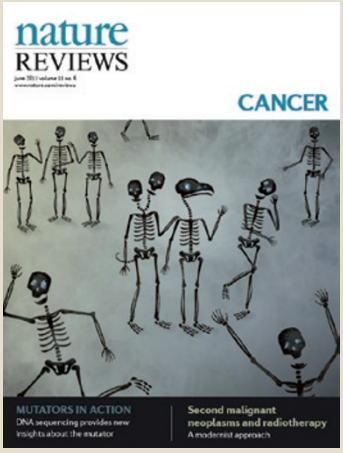

▶ **COVER:** 'Mutated two' by Lara Crow, inspired by the Perspective on p450, which describes the mutator phenotype.


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Disagreement between scientists is an important avenue through which our understanding of biological complexity improves. One polarizing area of cancer research is the role of genomic instability in tumour initiation and progression.Does it drive the acquisition of beneficial mutations? Or is it simply a result of the harsh tumour microenvironment, which causes DNA damage?

One scientist who has promoted the concept of genomic instability — specifically genetic instability — in driving tumour progression is Lawrence A. Loeb. Almost 40 years ago, Loeb and colleagues proposed that tumour cells have a mutator phenotype that allows them to progressively accumulate mutations, some of which are probably advantageous to the tumour cell. So, how has this hypothesis held up over the years? As discussed by Loeb on page 450, cancer genome sequencing projects have revealed a vast number of mutations in tumour cells. It is unlikely, of course, that these are all driver mutations, and such findings do not indicate that a cell can tolerate any number of mutations — most mutations probably have no effect and too many is probably lethal — but some level of mutagenesis could contribute, albeit incrementally, to tumour heterogeneity and the acquisition of new properties. The debate stimulated by such findings and hypotheses can generate insightful questions. For example, when questioning the relevance of the mutator phenotype one might consider how many mutations are required for tumorigenesis, tumour progression and metastasis. Furthermore, might metastases have a higher mutation rate than primary tumours and, if not, does that tell us that the mutator phenotype is wrong or that metastases might evolve differently?

There is no doubt that this debate will continue, much like our series on 'Genomic instability in cancer' to which this Perspective is the latest addition.

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