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Cancer found to be a moving target

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Cancer is the result of Darwinian evolution among populations of cells, in which the fittest cells win the struggle for survival, while ultimately killing the person of whom they are a part.

The mutator hypothesis, which states that normal human cells increase their rate of genetic change as a mechanism for speeding up the transformation to cancer cells, has been a pivotal concept in cancer biology for over 30 years, influencing our ideas both of how cancer arises and of the challenges of developing cancer therapies.

According to this hypothesis, an early step in becoming a cancer cell is a "mutator mutation", which causes the developing cancer to become genetically unstable. This accelerates the transformation of normal cells to cancer cells. It means that cancer cells are constantly changing, making them an elusive target for therapy.

However as a general concept applicable to all cancer, the mutator hypothesis has been debated on several grounds. Firstly, an increased mutation rate due to a mutator mutation could lead to an increased rate of random mutations that might reduce the fitness of the cell and its daughter cells (the "cell lineage") to compete for survival, dooming it to extinction before it could become malignant. Secondly, rates of cancer appearance in people can possibly be explained without a mutator mutation, just by continuing mutation at normal rates, and growth and selection of cell lineages with increased fitness; that is, by normal evolution occurring in populations of cells.

In an article published in the open-access journal *PLoS ONE*, Robert A. Beckman, a Visitor in the Simons Center for Systems Biology at the Institute for Advanced Study in Princeton, New Jersey, mathematically analyses the mutator hypothesis and compares the cancer-generating efficiency of mutator and non-mutator pathways to cancer, taking into account representative fitness changes a cell might experience as it potentially evolves to cancer. These fitness changes can be represented as pathways through a "fitness landscape", the equivalent of a topographic map of pathways to cancer.

Beckman had previously introduced the concept of efficiency in evaluating pathways to cancer. In previous work, he defined efficiency as the number of new cancer lineages expected to be created in the typical time it takes to develop cancer. He reasoned that, since most cancer cell lineages are eliminated by the body's defenses, or fail to establish a blood supply, the most efficient pathways to cancer would likely be the ones responsible for most cancers in people. He then showed that in the special circumstance where there are no fitness changes, mutator pathways are the most efficient path to cancer, even though getting the mutator mutation is itself an extra step.

In the current work, he shows more generally that mutator pathways are in most cases the most efficient path to cancer, even in the presence of fitness changes from a variety of fitness landscapes, addressing the previous objections to the mutator hypothesis. He also shows that the mutation rate which most efficiently evolves normal cells to cancer cells is likely to be higher than the mutation rate which is most efficient for driving the evolution of species. These findings provide strong support for the mutator hypothesis.

If the mutator hypothesis is true, there may be implications for cancer therapy. Genetic instability may enable cancer cells to rapidly evolve resistance to therapy, or may even mean that minority cell populations

within a cancer are already primed to resist therapy. Cancers which show more genetic instability may more readily evade any given therapy, and may require different strategies for treatment.

Citation: Beckman RA (2009) Mutator Mutations Enhance Tumorigenic Efficiency across Fitness Landscapes. PLoS ONE 4(6): e5860. doi: 10.1371/ journal.pone.0005860
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