Bowel cancer turns genetic switches on and off to outwit the immune system, new study finds

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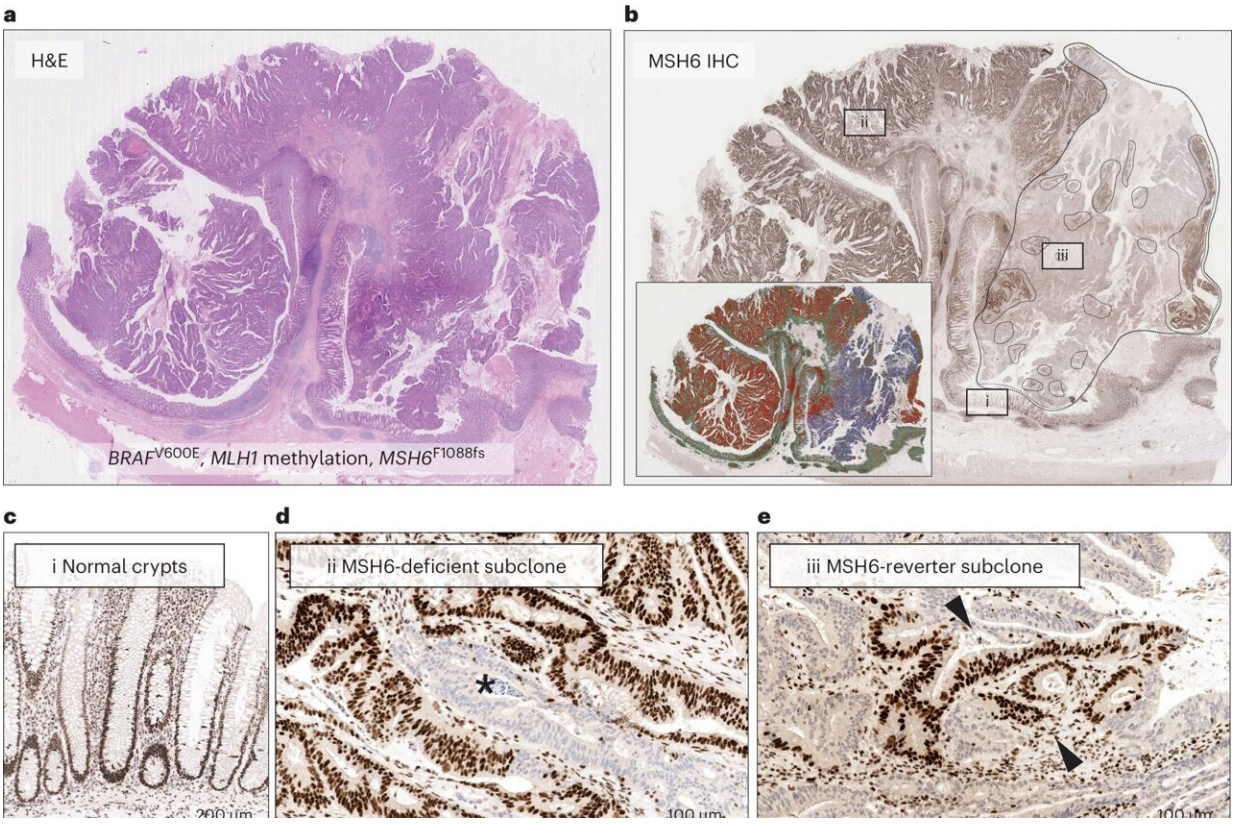

Frameshift switching of the MSH6 C8 coding homopolymer drives stochastic loss and restoration of MSH6 expression like a molecular ON/OFF switch. Credit: *Nature Genetics* (2024). DOI: 10.1038/s41588-024-01777-9

Bowel cancer cells have the ability to regulate their growth using a genetic on-off switch to maximize their chances of survival, a phenomenon that's been observed for the first time by researchers at UCL and University Medical Center Utrecht.

The number of genetic mutations in a cancer cell was previously thought to be purely down to chance. But a new study, published in *Nature Genetics*, has provided insights into how cancers navigate an "evolutionary balancing act."

The researchers found that mutations in DNA repair genes can be repeatedly created and repaired, acting as "genetic switches" that take the brakes off a tumor's growth or put the brakes back on, depending on what would be most beneficial for the cancer to develop.

Researchers say the findings could potentially be used in personalized cancer medicine to gauge how aggressive an individual's cancer is so that they can be given the most effective treatment.

Cancer is a genetic disease caused by mutations in our DNA. DNA damage occurs throughout life, both naturally and due to environmental factors. To cope with this, cells have evolved strategies to protect the integrity of the genetic code, but if mutations accumulate in key genes linked to cancer, tumors can develop.

Bowel cancer is the fourth most common cancer in the UK, with around 42,900 cases a year. Though still predominantly a cancer that affects older people, cases among the under 50s have been increasing in recent decades.

Disruption of DNA repair mechanisms is a major cause of increased cancer risk. About 20% of bowel cancers, known as mismatch repair deficient (MMRd) cancers, are caused by mutations in DNA repair

genes. But disrupting these repair mechanisms is not entirely beneficial to tumors. Though they do allow tumors to develop, each mutation increases the risk that the body's immune system will be triggered to attack the tumor.

Dr. Marnix Jansen, senior author of the study from UCL Cancer Institute and UCLH, said, "Cancer cells need to acquire certain mutations to circumvent mechanisms that preserve our genetic code. But if a cancer cell acquires too many mutations, it is more likely to attract the attention of the immune system, because it's so different from a normal cell.

"We predicted that understanding how tumors exploit faulty DNA repair to drive tumor growth—while simultaneously avoiding immune detection—might help explain why the immune system sometimes fails to control cancer development."

In this study, researchers from UCL analyzed whole genome sequences from 217 MMRd bowel cancer samples in the 100,000 Genomes Project database. They looked for links between the total number of mutations and genetic changes in key DNA repair genes.

The team identified a strong correlation between DNA repair mutations in the MSH3 and MSH6 genes, and an overall high volume of mutations.

The theory that these "flip-flop" mutations in DNA repair genes might control cancer mutation rates was then validated in complex cell models, called organoids, grown in the lab from patient tumor samples.

Dr. Suzanne van der Horst from University Medical Center Utrecht said, "Our study reveals that DNA repair mutations in the MSH3 and MSH6 genes act as a genetic switch that cancers exploit to navigate an evolutionary balancing act.

"On one hand, these tumors roll the dice by turning off DNA repair to escape the body's defense mechanisms. While this unrestrained mutation rate kills many cancer cells, it also produces a few 'winners' that fuel tumor development.

"The really interesting finding from our research is what happens afterwards. It seems the cancer turns the DNA repair switch back on to protect the parts of the genome that they too need to survive and to avoid attracting the attention of the immune system. This is the first time that we've seen a mutation that can be created and repaired over and over again, adding it or deleting it from the cancer's genetic code as required."

The DNA repair mutations in question occur in repetitive stretches of DNA found throughout the human genome, where one individual DNA letter (an A, T, C or G) is repeated many times. Cells often make small copying mistakes in these repetitive stretches during cell division, such as changing eight Cs into seven Cs, which disrupts gene function.

Dr. Hamzeh Kayhanian, first author of the study from UCL Cancer Institute and UCLH, said, "The degree of genetic disarray in a cancer was previously thought to be purely down to chance accumulation of mutations over many years. Our work shows that cancer cells covertly repurpose these repetitive tracts in our DNA as evolutionary switches to fine-tune how rapidly mutations accumulate in tumor cells.

"Interestingly, this evolutionary mechanism had previously been found as a key driver of bacterial treatment resistance in patients treated with antibiotics. Like cancer cells, bacteria have evolved genetic switches which increase mutational fuel when rapid evolution is key, for example when confronted with antibiotics.

"Our work thus further emphasizes similarities between evolution of

ancient bacteria and human tumor cells, a major area of active cancer research."

The researchers say that this knowledge could potentially be used to gauge the characteristics of a patient's tumor, which may require more intense treatment if DNA repair has been switched off and there is potential for the tumor to adapt more quickly to evade treatment—particularly to immunotherapies, which are designed to target heavily mutated tumors.

A follow-up study is already underway to find out what happens to these DNA repair switches in patients who receive cancer treatment.

Dr. Hugo Snippert, a senior author of the study from University Medical Center Utrecht, said, "Overall, our research shows that mutation rate is adaptable in tumors and facilitates their quest to obtain optimal evolutionary fitness. New drugs might look to disable this switch to drive effective immune recognition and, hopefully, produce better treatment outcomes for affected patients."

More information: Hamzeh Kayhanian et al, Homopolymer switches mediate adaptive mutability in mismatch repair-deficient colorectal cancer, *Nature Genetics* (2024). DOI: 10.1038/s41588-024-01777-9

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