'Collateral damage' from normal cell function may cause mutations that play a role in cancer

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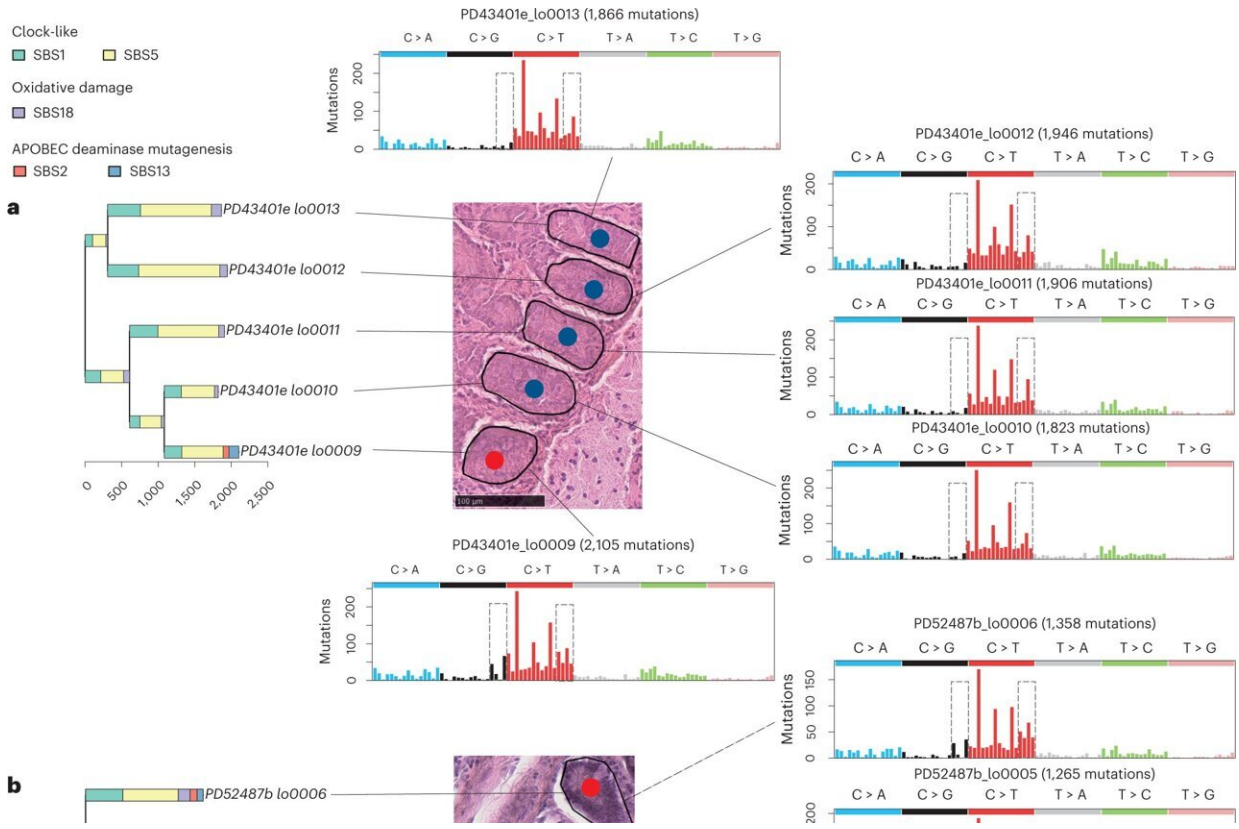

Spatial distribution of APOBEC-positive crypts. APOBEC-positive crypts and their surrounding crypts before microdissection with their SBS mutational spectrums. Signatures exposures are color coded on top left. Red dots, APOBEC-positive crypts. Blue dots, APOBEC-negative crypts that have been sequenced. Gray rectangles on the mutational spectra circle characteristic peaks of SBS2/SBS13. a, PD43401, this individual has one APOBEC-positive crypt but

all the remaining crypts in the neighborhood are negative. b, PD52487, with an APOBEC-negative crypt (PD52487b_lo0005) between APOBEC-positive crypts. c, PD45778, an APOBEC-negative crypt (PD45778b_lo0002) between APOBEC-positive crypts. Credit: *Nature Genetics* (2023). DOI: 10.1038/s41588-022-01296-5

The first comprehensive study of somatic mutations in normal human small intestine has been conducted by researchers at the Wellcome Sanger Institute and their collaborators. The findings revealed that an enzyme named APOBEC1 is likely responsible for two mutational signatures found in many cancers, SBS2 and SBS13, in the small intestine.

Published today in *Nature Genetics*, the research expands the members of the APOBEC family linked to SBS2 and SBS13. Because APOBEC1 performs a vital role in nutrient absorption in the small intestine, it is possible that high levels of SBS2 and SBS13 in the small intestine may be "collateral damage" caused by the normal functioning of cells.

Somatic mutations accumulate in cells during life. Though the majority of these mutations are harmless, some are known to be involved in diseases such as cancer. The biological processes that create mutations in normal cells, and the rate at which mutations occur, are not well understood.

But in recent years, researchers have taken advantage of technological advances to begin characterizing the landscape of somatic mutations in normal human cells across many tissue types. These studies have identified patterns of mutation, known as "mutational signatures," which provide insights into what "normal" somatic mutation looks like in different parts of the body and how they can lead to disease.

APOBEC is a family of enzymes that edit DNA or RNA. Mutations caused by the activity of these enzymes are common in many human cancers. Previous studies had focused on APOBEC3A and APOBEC3B as the primary generators of the mutational signatures SBS2 and SBS13 in human cancers.

In this new study, researchers set out to characterize the mutational landscape of the small intestine for the first time. In all, 342 individual small intestine crypts from 39 individuals were whole genome sequenced at the Wellcome Sanger Institute.

Analysis of somatic mutations in these tissues identified three mutational signatures found in most normal human cells: SBS1, SBS5 and SBS18. More surprisingly, it revealed that mutational signatures SBS2 and SBS13 were also common, which are rare in the large intestine and most other normal tissues.

"Previous research on the SBS2 and SBS13 mutational signatures in humans has generally focused on APOBEC3A and APOBEC3B. However, our findings show that in normal small intestine epithelium, APOBEC1 is the likely culprit. It could be that the high levels of SBS2 and SBS13 in this organ are 'collateral damage' caused by the high levels of APOBEC1 present, which are needed for the small intestine to do its normal job of absorbing and transporting nutrients," says Yichen Wang.

By retracing how each intestinal crypt developed from a single cell into several thousand, the researchers discovered fundamental information about somatic mutation in the small intestine.

"Our analysis reveals that APOBEC mutations occur in small bursts, with a single or very small number of episodes during the lifetime of an individual. The earliest instance we found was four years of age. The likely cause of APOBEC mutations in the small intestine seem to be due

to circumstances within the cell itself, rather than as a result of an external factor such as genotoxic metabolites produced by bacteria," says Dr. Philip Robinson.

"Though we have been studying somatic mutation in normal human cells for several years now, we continue to be surprised by what 'normal' looks like in the different tissues of the body. The discovery that APOBEC1 lies behind two important mutational signatures in the small intestine, rather than its better studied cousins, gives us cause to revaluate our understanding of APOBEC mutations more widely. Sometimes science throws up more questions than answers, but with each question we are one step closer to the truth," says Professor Sir Mike Stratton.

More information: Yichen Wang et al, APOBEC mutagenesis is a common process in normal human small intestine, *Nature Genetics* (2023). DOI: 10.1038/s41588-022-01296-5

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