

'Death clock' in cells could tell you when you'll get cancer

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Each tick of these clocks is a DNA mutation, and these build up at a constant rate throughout your life. The discovery will give us a deeper understanding of the causes of cancer, and an insight into healthy ageing. But here's the twist: if you could slow the rate at which these clocks tick, it might be possible to alter the rate of cancer – and even the rate at which we age.

Every cell in the body contains DNA, which acquires mutations – changes in individual genes – over time. Some of these mutations occur in bursts, say, from smoking or too much sun exposure. Others build up slowly over decades.

Some mutations seem to build up at a constant rate year by year, causing DNA damage, <u>which</u> <u>can lead to cancer</u>. Now, <u>Michael Stratton</u> at the Wellcome Trust Sanger Institute in Cambridge, UK, and his colleagues have identified two such mutational clocks in almost every cell in the body. They have also figured out how fast these clocks tick in different tissues.

They started by studying the DNA sequences of more than 10,000 individual cancers, encompassing 36 different types of cancer. An algorithm allowed them to search the cancer genomes for complex patterns of mutations – what they call signatures.

The team discovered more than 30 different signatures. Next, they looked at which of these occur in a clock-like manner, with the mutations appearing at a steady rate that correlates with the age of the person who provided the sample. Two signatures – numbers one and five – fitted

the bill. This also means they would have begun in healthy tissue <u>before it became cancerous</u>. "The cancer tissues are the cracked and dirty lens that allow us to look back in time to look at what's been happening in normal cells," says Stratton.

Faulty replicator

Cuba

Stratton's team believes signature one is a "mitotic clock", a mutation that occurs as a result of cell division. "The rate of mutations correlate with the rate of cell turnover in tissues," he says. "So in future we'll be able to use the number of mutations from this signature to know how many times a cell has divided – giving us a deep insight into the biology of human tissues."

Far less is known about signature five. Preliminary hypotheses suggest it may be linked to DNA repair. Over time, as DNA gets damaged it has to be patched up, which involves replicating small sections. "The machinery that replicates DNA occasionally makes mistakes and signature five might be the outcome of that," says Stratton.

For both signatures, the number of mutations correlated with the age of the person the sample came from. This allowed the team to figure out how fast the clocks were ticking in each tissue. For instance, signature one ticked quickest in stomach and colon cells – which resulted in about 23 mutations, per cell, per year, and slowest in breast and ovarian cells, which had three to four mutations per year.

Counting down

Because the clocks continue to tick once a healthy cell becomes cancerous, they could be used to tell how fast a cancer may metastasise and spread around the body, or become resistant to a drug, meaning doctors could plan the best course of action for a patient. They might even be used to predict cancer before it starts.

"It's not an inevitability for an individual to get cancer, but it's an inevitability for us as a species," says Stratton. "We accumulate mutations over a lifetime and in some people the correct combination leads to a cancer emerging. Further research will discover if our mutation rates differ between individuals. If that is the case, the expectation would be that those rates could be read out to predict the time they might take to become cancerous."

Stratton adds that in theory if you could alter the rate at which the mutations are occurring you might be able to change the rate at which cancer occurs. "I'm not saying this as a definite possibility – these mutations are so deeply embedded in our biology – but nevertheless this discovery inevitably leads you onto that kind of thinking. Every time we find something that causes cancer we think about how we can reduce it."

Is it possible then that human ageing could also be predetermined by one or both of these clock processes? The answer depends on the extent to which ageing is determined by the accumulation of mutations in individual cells, says Stratton. "If so, then certainly these two processes could contribute to ageing and their presence at a constant rate could predetermine the rate of ageing."

<u>Darryl Shibata</u>, at the USC Norris Comprehensive Cancer Centre and Hospital in Los Angeles, California, says that the team's work is important because there is high interest in discovering which mutations best represent age-related processes. "Ageing is fundamental to health and



many diseases," he says. "This is a fantastic paper."