Mutation order reveals what cancer will do next

- 18 February 2015 by **Andy Coghlan**
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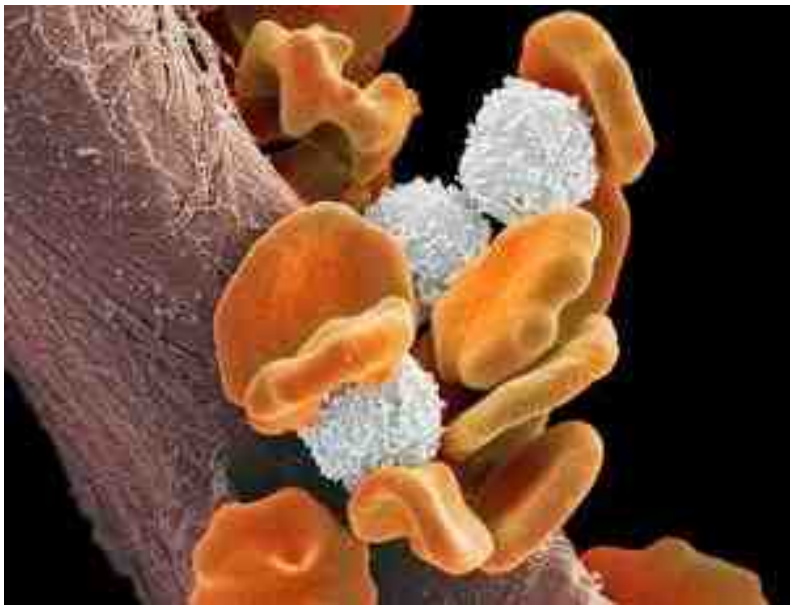

IT IS well known that cancers can develop from mutations in DNA – but now we've seen for the first time that a person's fate may depend on the order in which they occur.

In every cancer, there are hundreds of mutations, but some have more of an effect on the disease than others. It has now been shown that a cancer's path changes depending on which of these "driver mutations" comes first. This affects how the cancer develops, and which treatments are likely to work best.

This finding comes from an analysis of blood samples from 246 people with blood disorders called myeloproliferative neoplasms, which develop into leukaemia in about 5 to 10 per cent of cases. Researchers had access to samples from both early and later stages of the disease, enabling them to see the order in which key mutations appeared in affected blood cells.

"It's the first time we've been able to show that the order impacts both the clinical and biological features of the disease," says David Kent of the Cambridge Institute for Medical Research in the UK, and a lead author of the study (*The New England Journal of Medicine*, doi.org/z9f). "Before, we didn't know that order mattered."

Kent and his colleagues focused on mutations in two genes already known to be critical for development of this type of pre-leukaemia. A mutated *JAK2* gene sends production of red blood cells and platelets into overdrive. *TET2* normally helps kill abnormal stem cells, but when it mutates, unhealthy cells slowly build up in the bone marrow.

A tenth of the initial 246 blood samples had both mutations. Of these, the team identified 12 samples in which *TET2* had unequivocally mutated first, and another 12 in which the *JAK2* mutation came first.

By taking further samples from these people and tracking their symptoms, they were able to show that the disease took a different trajectory depending on which mutation came first.

They found that disease was noticeable 10 years earlier in people with *JAK2*-first mutations, because they were overproducing blood cells at high levels from the outset. In cell culture, these mutants were easier to kill with targeted *JAK2* inhibitor drugs than cells from those with *TET2*-first mutations, but Kent's team has yet to test that this is also true inside the human body.

By contrast, the disease was more hidden in those who developed *TET2* mutations first and was more likely to develop into full-blown leukaemia, but people in this group were less likely to suffer or die from blood clots than those who developed *JAK2* mutations first. "It's not a case of one being milder than the other, but that they drive disease in different directions," says Kent.

"This is a landmark study," says Charles Swanton of Cancer Research UK's London Research Institute. "It's the first to conclusively demonstrate that the order in which two driver events occur influences the subsequent evolution of the tumour, the underlying biological behaviour, type of disorder and clinical presentation of the disease," he says.

If the effects of mutation order were established for all common cancers, it could have a dramatic impact on treatment, says Kent. Doing this is likely to be easiest for cancers for which regular early biopsies are taken, such as breast and prostate cancer.

"We hope that our study will stimulate the search in other cancers for whether or not the order of mutation acquisition matters," he says.