Order matters: Sequence of genetic mutations determines how cancer behaves

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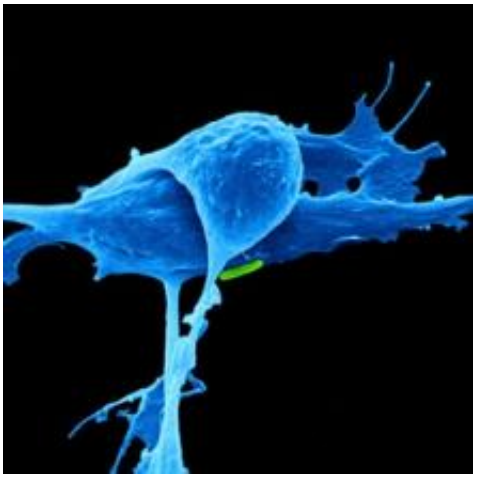

The order in which genetic mutations are acquired determines how an individual cancer behaves, according to research from the University of Cambridge, published today in the *New England Journal of Medicine*.

Most of the genetic mutations that cause cancer result from environmental 'damage' (for example, through smoking or as a result of over-exposure to sunlight) or from spontaneous errors as cells divide. In a study published today, researchers at the Department of Haematology, the Cambridge Institute for Medical Research and the Wellcome Trust/Medical Research Council Stem Cell Institute show for the first time that the order in which such mutations occur can have an impact on

disease severity and response to therapy.

The researchers examined genetically distinct single stem cells taken from patients with myeloproliferative neoplasms (MPNs), a group of bone marrow disorders that are characterised by the over-production of mature blood cells together with an increased risk of both blood clots and leukaemia. These disorders are identified at a much earlier stage than most cancers because the increased number of blood cells is readily detectable in blood counts taken during routine clinical check-ups for completely different problems.

Approximately one in ten of MPN patients carry mutations in both the JAK2 gene and the TET2 gene. By studying these individuals, the research team was able to determine which mutation came first and to study the effect of mutation order on the behaviour of single blood stem cells.

Using samples collected primarily from patients attending Addenbrooke's Hospital, part of the Cambridge University Hospitals, researchers showed that patients who acquire mutations in JAK2 prior to those in TET2 display aberrant blood counts over a decade earlier, are more likely to develop a more severe red blood cell disease subtype, are more likely to suffer a blood clot, and their cells respond differently to drugs that inhibit JAK2.

Dr David Kent, one of the study's lead authors, says: "This surprising finding could help us offer more accurate prognoses to MPN patients based on their mutation order and tailor potential therapies towards them. For example, our results predict that targeted JAK2 therapy would be more effective in patients with one mutation order but not the other."

Professor Tony Green, who led the study, adds: "This is the first time that mutation order has been shown to affect any cancer, and it is likely

that this phenomenon occurs in many types of malignancy. These results show how study of the MPNs provides unparalleled access to the earliest stages of tumour development (inaccessible in other cancers, which usually cannot be detected until many mutations have accumulated). This should give us powerful insights into the origins of cancer."

Work in the Green Lab is supported in party by Leukaemia and Lymphoma Research and Cancer Research UK.

Dr Matt Kaiser, Head of Research at Leukaemia & Lymphoma Research, said: "We are becoming more and more aware that a cancer's genetic signature can vary from patient to patient, and we are becoming better at personalising treatment to match this. The discovery that the order in which genetic errors occur can have such a big impact on cancer progression adds an important extra layer of complexity that will help tailor treatment for patients with MPNs. The technology to do this sort of study has been available only recently and it shows once again how pioneering research into blood cancers can reveal fundamental insights into cancer in general."

Dr Áine McCarthy, Science Information Officer at Cancer Research UK, says: "The methods used in this pioneering research could help improve our understanding of how cancer cells develop mutations and when they do so. This interesting study suggests that the order in which genetic faults appear can affect how patients respond to different drugs - this insight could help doctors personalise treatment to make it more effective for each patient."

More information: Ortmann, CA and Kent, DG et al. The Impact of Mutation Order on Myeloproliferative Neoplasms. *NEJM*; 11 Feb 2015.