New molecular mechanism revealed for genetic mutations in aggressive cancer cells

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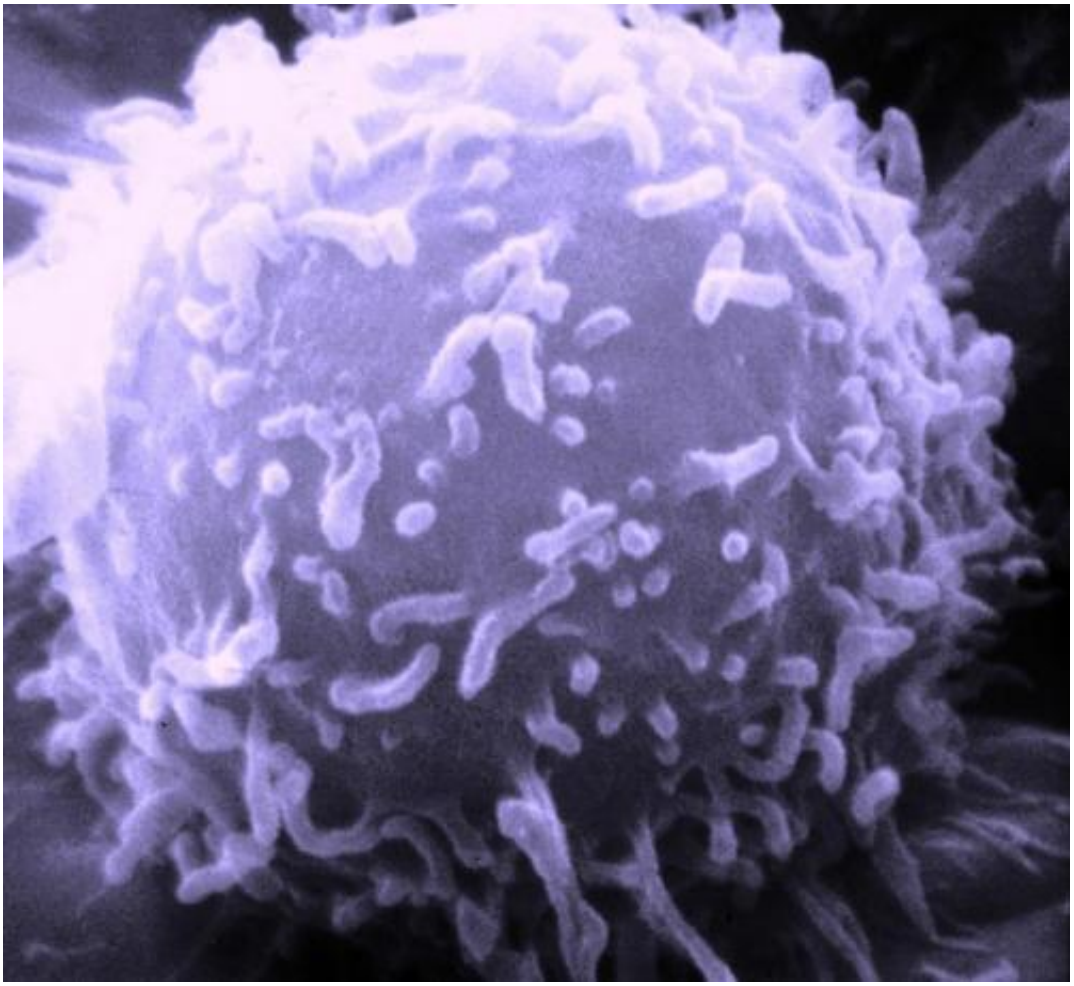

Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

Scientists at the University of Birmingham have described a previously-unknown molecular mechanism that could lead to the genetic mutations seen in certain types of aggressive cancer cells, involving a cell's own transcription machinery.

Genetic mutations are fundamental to the spread of cancer cells that form malignant tumours in the body. They are often caused by 'replication stress' within the cell, whereby DNA becomes damaged while it is duplicated. However, the underlying cause of this process has long been a mystery.

In a new study published today in *Nature Communications*, researchers reveal how replication stress (and subsequent genetic mutations) can be caused by an increase in activity of a cell's own transcription machinery.

The research shows that in cells with an activated version of the cancer-promoting gene (or 'oncogene') H-RasV12, the rate of transcription and protein production is dramatically increased. The resulting RNA can form unusual structures called 'R-loops' within the DNA of the cell, which in turn cause DNA damage and replication stress.

Although it was previously suspected that H-RasV12 caused increases in transcription, this study provides the first solid evidence of the mechanism, as well as the first description of the role of this oncogene in R-loop formation.

'This research is the first to show conclusively that an oncogene-induced boost in gene expression is enough to interfere with DNA replication,' says lead researcher Dr Eva Petermann, from the University of Birmingham's Institute of Cancer and Genomic Studies.

'Our findings help to create a new unified view of the roles of transcription and replication in the process of cancer cell mutations. This

is a big step in basic cancer biology, and potentially opens up a whole new area of research into transcription proteins and replication stress.'

A better understanding of replication stress may help improve the efficacy and application of a number of new cancer drugs currently undergoing clinical trials, including AstraZeneca's ATR and Wee1 inhibitors.

More information: Panagiotis Kotsantis et al. Increased global transcription activity as a mechanism of replication stress in cancer, *Nature Communications* (2016). DOI: 10.1038/NCOMMS13087

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