EMBARGOED UNTIL: Sunday 23 April, 13:00 EST; Monday April 24 03:00:00 AEST (Sydney)

Cancer cells suppress large regions of DNA by a reversible process that can be tackled with new therapies

Cancer researchers at Sydney's Garvan Institute, in collaboration with Spanish scientists, have formulated a new concept for how cancer cells can escape normal growth controls, which may have far-reaching implications for the new generation of cancer therapies.

They have found large regions of DNA are 'switched off' in colon cancer. Lead researcher Associate Professor Sue Clark, of the Garvan Institute, says: "These large regions – referred to as suburbs – contain genes that normally function to prevent the development of tumours".

Our cells become cancerous when the normal controls over cell growth and death go awry. This deregulation has traditionally been linked to DNA mutations of single genes or deletion of large sections of the chromosome. However more recently it has become clear that gene silencing in cancer can also occur, in the absence of changes to the DNA sequence: a phenomenon known as 'epigenetics'. DNA methylation is one of the main epigenetic processes.

In cancer, the DNA methylation pattern of many genes changes. However, until now, it was believed that only individual single genes were silenced by methylation. But this is not necessarily the case. "What we've found is that non-methylated genes that reside in a particular suburb near methylated genes are also silenced. Their physical proximity to the methylated genes affects their ability to function. It's a case of being in the wrong neighbourhood at the wrong time", says Assoc. Professor Clark.

The Garvan team developed a new method to scan the entire complement of the 30 000 plus genes – the entire genome – in the cancer tissue samples, which allowed widespread changes to be identified in specific parts of the genome.

They were amazed to find the extent of gene silencing. Assoc. Professor Clark adds: "What we want to do now is determine if these same regions are switched off in other types of cancers".

The team also hope that new cancer therapies, which can reverse DNA methylation, will restore the cell's normal regulation and treat and prevent cancer.

Notes for editors:

There are already compounds that promote DNA demethylation that are in clinical trials. This research explains how some of the new cancer therapies will work and how they may have far greater effects than first envisaged.

This paper will be published online in Nature Genetics on Sunday, April 23, 1pm EST.
http://dx.doi.org/10.1038/Ng1781

"Epigenetic remodelling in colorectal cancer results in co-ordinate gene suppression across an entire chromosome band". Jordi Frigola, Jenny Song, Claire Stirzaker, Rebecca A Hinshelwood, Miguel A Peinado, & Susan J Clark.

BACKGROUND

The term 'epigenetics' refers to heritable (passed on from parent to child) DNA changes that alter the function of a gene without changing the DNA sequence. Chemical processes such as methylation can cause epigenetic changes where small molecules are reversibly attached onto a gene. The extent to which genes are methylated is a means of controlling when and how much of a protein is produced from a gene. Identical twins with the same DNA may even develop different diseases because of epigenetics.

In cancer, the DNA methylation pattern of many genes changes. Genes that regulate normal cell growth – such as tumour suppressor genes – can be 'silenced' by DNA methylation. Methylation is a reversible process and as such is a good target for molecular-based cancer therapies.

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