Getting down to cancer basics

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Researchers have identified a new cancer gene - one that is common to many cancers and affects the most basic regulation of our genes. The new example - a gene on the X chromosome called UTX - is found in 10% of cases of multiple myeloma and 8% of esophageal cancers.

UTX plays a role in overall regulation of the activity of many genes and it is possible that other genes with similar roles will also be found to be involved in different tumor types. This is the first example of mutations in a gene of this functional class. The finding arose from a study of mutations in 4000 genes in kidney cancer.

"UTX is an important component of the transcriptional control machinery - it influences some of the most fundamental mechanisms controlling gene activity in our cells," explains Dr Andy Futreal, co-leader of the Cancer Genome Project at the Wellcome Trust Sanger Institute. "Unlike many cancer genes, UTX does not appear to be directly involved in cell division or cell death but in basic gene regulation and shows the depths to which cancers will plumb in order to get themselves ready to go."

The normal UTX protein modifies part of the structure holding DNA together in our cells. The composite DNA-protein structure, called chromatin, is not simply a scaffold, but plays an active role in controlling gene activity. The UTX protein alters a key organising subunit component of chromatin, called a histone. The protein is likely to be involved in both turning genes on and off, making it a key regulator of the yin-yang of gene control.

In the massive DNA sequencing study, the team found rare mutations of the UTX gene in clear cell renal cancer - a type of kidney cancer. When they expanded the search they found mutations in many cancer types - including one in ten multiple myeloma and one in twelve esophageal cancer cases.

"This work shows that mutations in genes with different functions can be found in human cancer through systematic approaches. These results indicate that cancer genes are not restricted to 'classical' roles of survival and cell proliferation, but can affect a variety of other cellular mechanisms," explains Professor Victor Velculescu, Associate Professor of Oncology and Director of Cancer Genetics from the Ludwig Center at Johns Hopkins and co-Director of Cancer Biology, at Johns Hopkins Kimmel Cancer Center. "UTX wouldn't have been found without this high-throughput type of study and indicates the type of novel findings we might expect from the International Cancer Genome Consortium."

The International Cancer Genome Consortium (ICGC) seeks to catalogue genetic abnormalities in 50 different tumour types. The possibility of uncovering new regulatory genes - like UTX - along with continued efforts to catalog cancer genes, will boost researchers' attempts to comprehensively describe different cancers which will to lead to expanding opportunities to reduce the global cancer burden.

The team showed that the biology of the mutation fitted their prediction. Cells that lacked a functional UTX gene showed notable slowing of growth when a copy of normal UTX was reintroduced. As well, substantial changes in gene transcription were noted. Genes with the most significant changes in expression were highly enriched in those most susceptible to control by UTX mediated histone modification.

The work identifies a new class of cancer genes that researchers can now pursue. These are genes that occupy the central control position of gene activity and act to keep cells from turning cancerous. When such 'tumor suppressor genes' are inactivated, other genes can run riot.

The consequence of mutation in UTX is to bring about changes in activity of other genes through epigenetic changes - their activity is changed by modification, not of their DNA code, but of their

associated proteins and chemical tags.

"This is a genetic change with consequences at the level of epigenetic regulation," explains Professor Mike Stratton, co-leader of the Cancer Genome Project at the Sanger Institute. "When we look at cancers, a substantial proportion of the epigenetic disregulation may well have a genetic basis."

Histone biology

DNA is not simply dissolved in our cells, but interacts with many proteins in structures that influence gene activity. Chromatin, the most-studied DNA-protein structure, consists largely of DNA in association with five classes of proteins called histones.

Histones bind strongly to DNA and interact with one another to produce the compact structure of chromatin. The strength of the association of histones with DNA can be modified by the addition or removal of simple chemical groups (such as methyl or acetyl groups) to or from the DNA.

Enzymes, such as the protein specified by the UTX gene, alter the levels of histone modification and so can alter activity of many genes.

More information: Van Haaften G et al. (2009) Somatic mutations of the histone H3K27 demethylase, UTX, in human cancer. *Nature Genetics* Published online before print as doi:10.1038/ng. 349

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