



A step towards finding the cancer switch

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Sydney epigeneticists believe they are one step closer to locating the switch that turns on cancers.

Epigenetics, the biochemical processes that 'switch on' bad genes and 'switch off' good ones, inhabits in an infinitesimal universe.

The nucleus of each cell in our body contains two metres of DNA, roughly 30,000 genes, compacted very tightly.

Understanding the processes that take place inside those strands of DNA will help us control them, unleashing great advances in medicine, particularly the treatment of cancer.

PhD student Rebecca Hinshelwood and Professor Susan Clark at Sydney's Garvan Institute of Medical Research in Sydney believe they have solved a central puzzle. Their findings, which describe how the breast cancer suppressor gene P16 is silenced, are published online in the current issue of *Human Molecular Genetics*.

"We are very much working in the outer space of the cell," said Professor Clark, leader of the project. "We're zooming into these tiny changes that then trigger the remodelling of the gene."

"Capturing that moment of change is critical, when a normal cell starts to become a cancer cell. Just before and during the very first cell division."

When you look at a strand of DNA down a very powerful microscope, you see what looks like beads on a string. The beads, known as 'nucleosomes', are small proteins that help the long strand of DNA coil into the smallest space possible. Exactly 160 'base pairs' of DNA wrap around each nucleosome, followed by a 50 base pair stretch of uncoiled DNA, or 'linker'. The whole genome is organised in this 'higher order structure'.

While you can see the bead and string shape of DNA under a microscope, you cannot see the molecular processes that take place inside. For that, epigeneticists must measure and analyse biochemical changes, including 'methylation' (when groups of molecules attach to DNA and literally cause it to scrunch up, or close down).

Clark explained that members of her lab have been able to map the process of methylation in three dimensions and show that "it targets the string between the beads first, what we call the 'linker' region of DNA. It then goes on to spread around the nucleosomes, or beads."

“There’s been a chicken and egg debate in the literature for some time. Which comes first, methylation or silencing. As it happens, we find that they work in tandem, like a crank. A bit of methylation, a bit of silencing. A bit more methylation, a bit more silencing. Until the gene shuts down permanently.”

“Obviously, when a tumour suppressor gene shuts down, cancers can form. While we looked specifically at a breast cancer suppressor gene in our study, our finding applies to all cancers.”

“The dream of every cancer researcher is that one day we will be able to turn off the cancer switch.”

Unlike genetic alterations, epigenetic changes can be reversed. Methylation, for example, can be eliminated by epigenetic drugs. Good genes can be switched on again, bad ones switched off.

There are various epigenetic drugs in clinical trials at the moment.

ABOUT GARVAN

The Garvan Institute of Medical Research was founded in 1963. Initially a research department of St Vincent's Hospital in Sydney, it is now one of Australia's largest medical research institutions with nearly 500 scientists, students and support staff. Garvan’s main research programs are: Cancer, Diabetes & Obesity, Immunology and Inflammation, Osteoporosis and Bone Biology, and Neuroscience. The Garvan’s mission is to make significant contributions to medical science that will change the directions of science and medicine and have major impacts on human health. The outcome of Garvan’s discoveries is the development of better methods of diagnosis, treatment, and ultimately, prevention of disease.

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