



Cancer study overturns current thinking about gene activation

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A new Australian study led by Professor Susan Clark from Sydney's Garvan Institute of Medical Research shows that large regions of the genome – amounting to roughly 2% – are epigenetically activated in prostate cancer.

Regions activated contain many prostate cancer-specific genes, including PSA (prostate specific antigen) and PCA3, the most common prostate cancer markers. Until now, these genes were not known to be regulated epigenetically.

A previous study from Professor Clark's lab showed that similarly large regions of the prostate cancer genome are also epigenetically silenced, demonstrating a structured rearrangement of the cancer epigenome.

Epigenetics looks at biochemical changes that affect how the genome is organised in the cell nucleus, which in turn controls how genes are expressed. Attachment or detachment of certain molecules can literally open or close DNA's structure, allowing a gene to be expressed if the structure is opened, and silenced if the structure is closed.

Among other aspects of epigenetic activation, the new study shows that the epigenetic process known as 'methylation' can activate genes, often by changing the gene start site, overturning the prevailing dogma that DNA methylation can only silence genes.

The findings as a whole have extensive ramifications for cancer diagnosis and treatment, including epigenetic-based gene therapies, as they require the targeting of domains of genes, as opposed to single genes.

PhD student Saul Bert and Professor Clark used gene expression profiling data and genome-wide sequencing technology from prostate tumour cells to determine which parts of the genome were epigenetically activated in prostate cancer. They then examined the mechanisms behind activation, publishing their findings in the very prestigious international journal *Cancer Cell*, now online.

DNA is made up of building blocks of nucleic acid known as 'base pairs', specifically guanine-cytosine (GC) and adenine-thymine (AT). Unlike other parts of the genome, there are dense clusters of CG pairs very close to gene start sites. These CG clusters, known as 'CpG islands', are where methylation occurs.

"When I started my PhD, we were looking to see if there was loss of methylation at CpG islands, causing gene activation in cancer," said Saul Bert.

“We took a whole genome approach, looking at all the gene transcription start sites that included CpG islands. What we saw surprised us, because we saw gene activation at hypermethylated sites – that went against current thinking.

“We went on to show in the lab that if you methylate CpG islands that are very close to transcription start sites, but not exactly on top of them, then it’s possible to turn genes on.

“While the realisation that methylation can trigger gene activation represents a paradigm shift in thinking, our other finding - that the prostate cancer genome contains domains that harbour multiple gene families, tumour related genes, microRNAs and cancer biomarkers – is equally important. These domains are simultaneously switched on through significant epigenetic remodelling.

“In this study, we identified 35 domains including 251 genes. While the genes may seem to be functionally unrelated, their coordinated regulation in the cancer genome suggests the presence of epigenetic 'master controllers' that can switch on or off very large regions of DNA.”

Project leader Professor Clark believes the study will have a significant impact on our understanding of diagnostic tests and on chemotherapy treatment.

“What we are seeing in prostate cancer would apply to other cancers. The big new finding is about the ways in which neighbouring genes are being co-ordinately activated in cancer,” said Professor Clark.

“The increased expression is not just due to genetic amplification – but we now show is also due to unraveling of the cancer genome.

“We need to understand this process more deeply to determine the impact of current epigenetic therapies that are aimed at promoting gene activation rather than suppressing oncogene expression.”

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 over 600 scientists, students and support staff. Garvan's main research areas are: Cancer, Diabetes & Obesity, Immunology and Inflammation and Neuroscience. 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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