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Research provides new kidney cancer clues

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Researchers have identified a gene that is mutated in one in three patients with the most common form of renal cancer. The identification of a frequently mutated gene will provide new insights into the biology of the disease. This biological knowledge will be critical in the continued effort to improve treatment for renal cancer.

The gene – called PBRM1 – was found to be mutated in 88 cases out of 257 clear cell renal cell carcinomas (ccRCC) analysed, making it the most prevalent to be identified in renal cancer for 20 years. The study was carried out by researchers from the Wellcome Trust Sanger Institute, the Van Andel Research Institute, USA, and the National Cancer Centre of Singapore.

The mutations all appear to inactivate a protein which plays a role in remodelling the structure of the genetic material, allowing access of the DNA code to other proteins that can repair damage, control cell growth and turn other genes on and off.

Treating ccRCC is confounded by the fact that tumours can grow in the kidney without symptoms for some time before they are recognised. Survival rates for tumours recognised early in their development can be as high as 95 per cent, but that prognosis falls over time as tumours develop. For many years, the main genetic determinant known to be involved in the development of renal carcinoma was mutation of the VHL gene on chromosome 3.

"Until recently, when we talked about the genetics of renal carcinoma we

would inevitably be talking about VHL – a gene mutated in eight out of ten patients," says Dr Andy Futreal, Head of Cancer Genetics and Genomics and co-Head of the Cancer Genome Project at the Wellcome Trust Sanger Institute. "But we knew this was likely not to be the full story – so the question we have sought to answer is which genes are conspiring with VHL to cause the disease we see in patients?

"Over the last year or so, we have started to assemble that puzzle – this research provides a new and critical piece."

The team's recent work had previously identified three mutated genes associated with renal cancer. These genes are all involved in altering part of the scaffold – known as chromatin – that holds the DNA together in our cells and can influence gene activity. By altering a component of this scaffold, called a histone, the genes play a role in controlling other genes and managing how cells can divide and repair. Although these discoveries had provided a crucial glimpse of a new biological route into renal cancer, mutations in these genes only contribute in a relatively small number of cases.

Importantly, the newly discovered gene, PBRM1 (also known as Baf180), functions as part of a protein complex called SWI-SNF, which also acts to alter the structure of chromatin – further pointing to the importance of genome regulation in renal cancer.

"Over the last year, our understanding of how kidney cancer develops had already markedly improved through identification of three new mutated cancer genes, each of which makes a small contribution to the disease" says Professor Mike Stratton, Director of the Sanger Institute and co-Head of the Cancer Genome Project. "Now, our discovery of PBRM1 mutations in one in three kidney cancers is a major advance. We think we may have an almost complete understanding of the set of abnormal genes that drive this cancer and our understanding of the

disease has been transformed by the realisation that most of these genes are involved in providing the structure that encases DNA in the cell and that regulates its function. This insight will provide us with many new therapeutic directions for this cancer."

Much of the story, the researchers suggest, seems to be is locked into a small region of chromosome 3.The study finds that PBRM1 is tied together with two previously identified renal cancer genes – including the well-established VHL cancer gene and the recently identified gene SETD2 – on a small region of chromosome 3.

The team suggests that the fact that the genes are linked in their location allows cancer to exploit our biology – by reducing the number of genetic events needed to hit and inactivate all three genes. The team found a significant level of overlap, with many patients carrying mutations in two, if not all three of the genes in this region.

"This study has begun to unlock the way these latest gene discoveries contribute to cancer," says Professor Bin Tean Teh from the Van Andel Research Institute, USA and National Cancer Centre of Singapore. "And it is to the cancer's advantage that they sit together. The challenge for the future will be to build a picture of the processes the genes control. That will mean looking beyond the linear DNA code to the chemical interactions that take place at the structural level – at the level of the chromosome."

To begin to build a biological picture of the impact of PBRM1, the team looked at the results of experiments previously carried out in the mouse.

"By looking at the mouse, we can make the critical leap from establishing statistical association to exploring biological causation," says Dr David Adams, Head of the Experimental Cancer Genomics team at the Wellcome Trust Sanger Institute. "Our experiments in the mouse

suggest that PBRM1's role as a cancer gene is not restricted to renal cancer. We find that Pbrm1 is also seen in the pancreatic cancers in the mouse.

"This finding reinforces the need to define cancer not just by the organ, but also by the mutational profile of individual patients."

As well as the PBRM1 mutations, the team also found mutations in a gene called ARID1A in some ccRCC cases. The same gene was identified just weeks ago in clear cell ovarian cancer. The researchers suggest that further larger-scale research will be needed to understand what role this second gene plays in renal cancer.

More information: Varela I et al. (2010) Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma. *Nature*. Published online before print at doi:10.1038/nature09639

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