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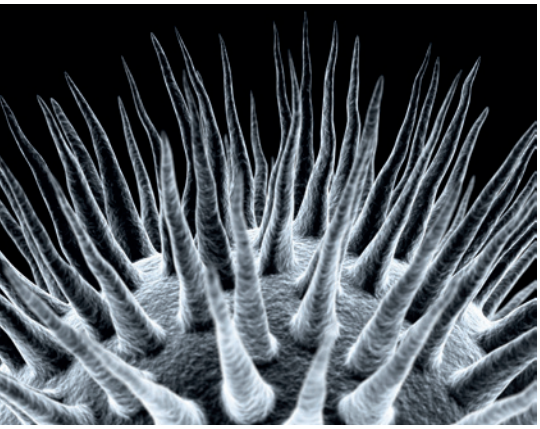
GENETICS

Identifying driver mutations with the help of viruses

"Could viral proteins be used as stand-ins for identifying proteins—and the underlying gene mutations—associated with cancer?" So asked Michael Cusick of the Center for Cancer Systems Biology at the Dana–Farber Cancer Institute, speaking for a multidisciplinary team who recently showed that yes, oncogenic viruses can be used to identify tumorigenic mutations in human cells.



This hypothesis was founded on the knowledge that oncogenic viruses alter their host genetic and proteomic networks in much the same way that genetic variations perturb cellular processes to drive cancer. The researchers mapped viral protein–human protein interactions in three ways, using human papillomavirus, Epstein–Barr virus, adenovirus and polyomavirus proteins. Genome-scale yeast two-hybrid screens revealed 454 binary interactions between 53 viral proteins and 307 human proteins. Next, they constructed a co-complex 'interactome' network to show the physical associations between the viral and human proteins using tandem affinity purification (TAP) and mass spectrometry. This analysis yielded 3,787 viral–host co-complex associations. Lastly, they characterized transcriptional perturbations induced by the viruses on the genome scale using microarray analyses on TAP-tagged cell lines expressing viral proteins.

Cross-referencing these data against a panel of genes thought to be causative in human cancer revealed considerable overlap, showing the strength of the viral strategy in identifying genes involved in cancer. More than 900 host target genes were eventually compiled into a candidate set of causative cancer genes, the so-called VirHost set. The authors concluded that using multiple approaches to home in on the causative genes in human cancer increases the likelihood these genes are in fact drivers of cancer, and not merely bystanders. Consequently, we might well now have a clearer set of genes and gene products to investigate as potential therapeutic targets for multiple cancer types.

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Original article Rozenblatt-Rosen, O. *et al.* Interpreting cancer genomes using systematic host network perturbations by tumour virus proteins. *Nature* doi:10.1038/nature11288