GENOMICS

# Driving cancer biology

BRAND X

Identifying genes as drivers of tumorigenesis from cancer genomics analyses is a crucial challenge. Dana Pe'er and colleagues have developed a new algorithm, copy number and expression in cancer (CONEXIC), to identify genes that exhibit copy number alterations (CNAs) that drive tumorigenesis.

CONEXIC relies on the idea that driver genes (or modulators) are disproportionately expressed as they provide a fitness advantage to the tumour, and on the idea that the expression of driver genes directly or indirectly affects the expression of groups of genes, termed modules, to produce a specific biological effect. By analysing both CNAs and the expression of genes in cancer tissue samples, and by ranking them according to biological function, the authors have generated an unbiased method for identifying drivers that best account for the behaviour of the modules.

> "CONEXIC seems to effectively identify drivers of tumorigenesis, the genes affected by these drivers and their possible functions."

The authors applied CONEXIC to a previously published data set of paired gene expression and CNA data from cultured melanoma samples. They identified 64 ranked modulators that explained the expression characteristics of 7,869 genes. Of the top 30 modulators, ten were known oncogenes and tumour suppressor genes. An automated literature analysis (LitVAn) was then used to assign functional information to the modulators and their associated modules. Of the 30 modulators, key terms that were identified included PI3K, MAPK, cyclin and Rab. Rab GTPases regulate membrane transport and vesicular trafficking, and these processes have not previously been associated with melanoma. The list of modulators and associated modules were validated with two other cohorts of melanoma samples, and 80% of the modulators were conserved between data sets. Microphthlamia-associated transcription factor (*MITF*) was identified by CONEXIC as the highest ranked modulator of melanoma. MITF has previously been associated with melanoma, and its expression correlates with reduced survival, further validating this approach. The authors tested the validity of the modules that were generated by the algorithm, and they found that 76 of the 80 published MITF targets were classified as MITF modules by CONEXIC, suggesting that CONEXIC could be relied on. Thus, the authors went on to assess some of the less well-known modulators that were identified.

Ranked second in the list of modulators was *TBC1D16*, which encodes a Rab GTPase-activating protein of unknown function. To clarify the function of TBC1D16 in melanoma, the authors looked to the associated modules, which mostly regulated melanogenesis, trafficking, survival and proliferation. Consistently, knock down of *TBC1D16* in two melanoma samples from the original data set that overexpressed this gene substantially reduced cell growth, but there was no effect in cells that did not overexpress *TBC1D16*. Another modulator identified by the CONEXIC analysis was *RAB27A*, which functions in melanosome trafficking. Again, knock down of *RAB27A* reduced melanoma growth, particularly in those samples that overexpressed this gene. Moreover, the three modules that were predicted to be associated with *RAD27A* were differentially expressed when *RAD27A* was knocked down, lending further support to the CONEXIC predictions.

CONEXIC seems to effectively identify drivers of tumorigenesis, the genes affected by these drivers and their possible functions. Indeed, a previously unknown role of vesicular trafficking in melanoma has been identified using this method. However, it is important to note that CONEXIC cannot detect mutated oncogenes or tumour suppressor genes that drive tumorigenesis, such as *NRAS* and *BRAF*.

*Gemma K. Alderton*

**ORIGINAL RESEARCH PAPER** Akavia, U. D. *et al.* An integrated approach to uncover drivers of cancer. *Cell* **143**, 1005–1017 (2010)