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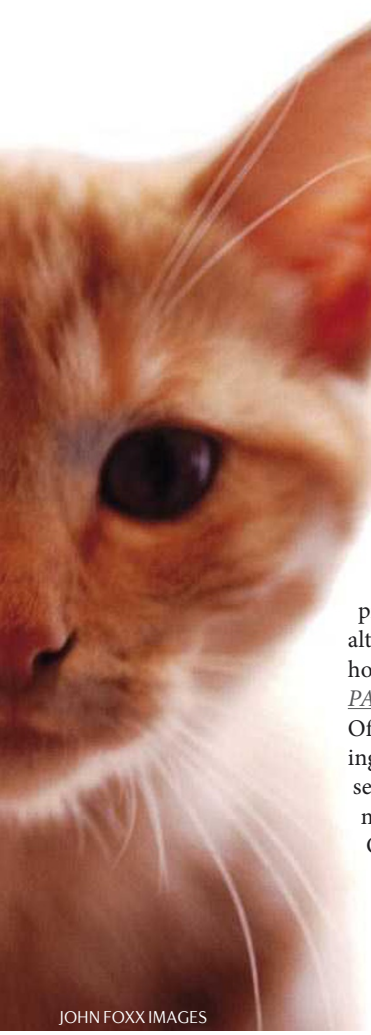
GENETICS

More than one way....


JOHN FOXX IMAGES

Now that the human genome has been sequenced, researchers — aided by the rapid development of high-throughput sequencing platforms, as well as other large data analysis systems — can begin to track and understand all genetic changes occurring within a specific type of tumour.

The Cancer Genome Atlas aims to discover and catalogue major cancer-causing genomic alterations by assessing multiple human tumour samples. Glioblastoma, the most common primary brain tumour in adults, is one of the first tumour types to be analysed. DNA and RNA extracted from 206 samples of primary glioblastoma, including 21 samples from patients who had been treated for their disease, were analysed for DNA methylation status and copy number aberrations, as well as coding and non-coding RNA expression. These integrative analyses identified alterations in genes known to be causative in this disease, such as receptor tyrosine kinases (in particular Erbb family members), those that are part of the phosphoinositide 3-kinase pathway (*PIK3CA* and, surprisingly, *PIK3R1*) and components of the p53 and RB tumour suppressor pathways. However, novel alterations were also seen, such as homozygous deletion of *NF1* and *PARK2* and amplification of *AKT3*. Of these tumour samples 91 (including 19 treated) were selected for sequencing to determine somatic mutations in 601 selected genes. Of these, 223 genes were found to have non-silent mutations, 79 of which had more than one mutation. Interestingly, the mutation rate differed markedly between untreated and treated patients, with 7 of the treated patients having a hypermutated phenotype. Importantly, an unexpected relationship was observed between methylation of the *MGMT* promoter (a DNA repair enzyme), patients with a hypermutator phenotype who were previously treated with alkylating therapy (temozolomide and/or CCNU), and disruption of the DNA mismatch repair pathway (6 out of 7 of the hypermutated tumours). Thus, although methylation of *MGMT* predicts sensitivity to temozolomide, this type of treatment seems to select for disruption of the mismatch repair pathway as a mechanism of resistance. Given that temozolomide is part of the current standard of care for patients with glioblastoma, this finding, if proved, will have significant clinical impact.

Another consortium of researchers, including Bert Vogelstein, Victor Velculescu and Kenneth Kinzler, used sequencing and gene expression analyses to investigate mutations in glioblastoma and pancreatic cancer. Using 22 human glioblastoma samples, they sequenced 20,661 protein-coding genes and analysed the same samples for genomic changes as well as gene expression changes. They noted that the sample from the one patient who had been treated with temozolomide and radiation had 17-fold more alterations than the untreated patients and that the mutation spectrum was also dramatically different. Analysis of the 21 untreated samples showed that 685 genes had one or more non-silent mutations, with a mean of 47 mutations per tumour. This was less than previously established for colorectal or breast tumours, suggesting that glioblastoma arises after fewer cell divisions than these epithelial cancers. Combined assessment of the sequencing, copy number and gene expression data identified the mutations most likely to drive cancer development. These included changes to genes involved in the pathways mentioned above as well as changes in genes that regulate neuronal cell-specific functions such as synaptic transmission and axonal guidance. Analysis of the individual gene data showed that isocitrate dehydrogenase 1 (*IDH1*), which is involved in the regulation of oxidative damage through production of NADPH, was mutated in 12% of all samples analysed. Of interest is the fact that this gene seems to be more often mutated in young patients (<35 years) and this correlated with an improved prognosis.

A similar series of analyses in 24 advanced pancreatic adenocarcinoma samples showed that 1,327 of the 20,661 genes sequenced had at least one mutation, with a mean of 48 per tumour. Interestingly, large genomic deletions are commonly found in pancreatic tumours, with *CDKN2A* (encoding INK4A and ARF), *TP53* and *SMAD4* being the most likely tumour suppressors to be selected against. Analysis of driver mutations identified a number of genes known to be associated with pancreatic cancer and many that are not. Differential gene expression analyses also showed that 541 genes were overexpressed, 54 of which encode secreted or cell surface proteins, making them potential diagnostic markers and therapeutic targets. The authors developed an algorithm to link the genetic mutations to different cellular pathways and found that, although there are 12 core signalling pathways and processes that are disrupted in pancreatic cancer, the genetic changes responsible for them vary widely between individual tumours. Therefore, agents that target a pathway rather than a gene are likely to be more effective for the treatment of this cancer.

All three papers clearly show that unbiased systematic approaches can lead to a more comprehensive understanding of the changes that occur during tumour development and treatment.

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ORIGINAL RESEARCH PAPERS The Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature* 4 Sep 2008 (doi 10.1038/nature07385) | Williams Parsons, D. *et al.* An integrated genomic analysis of human glioblastoma multiforme. *Science* 4 Sep 2008 (doi 10.1126/science.1164382) | Jones, S. *et al.* Core signalling pathways in human pancreatic cancers revealed by global genomic analyses. *Science* 4 Sep 2008 (doi 10.1126/science.1164368)