FORUM Genomics

Comparisons across cancers

Analysis of cancer genomes is moving beyond the confines of a particular disease — researchers are now comparing the genetic and epigenetic characteristics of multiple tumour types. Two scientists comment on what such studies can teach us about cancer biology and how they may guide clinical practice. [SEE ARTICLE P.333](#)

THE PAPER IN BRIEF

- Research networks around the world are cataloguing DNA mutations, chemical changes to DNA-associated proteins, and expression of RNA transcripts and proteins in thousands of human tumours.
- In a series of 16 papers¹, one of which is published on page 333 of this issue (Kandoth *et al.*)², The Cancer Genome Atlas (TCGA) Research Network presents comparisons of such data across as many

as 12 tumour types (Fig. 1).

- The publications join other pan-cancer efforts in revealing commonalities between all cancer types, shared molecular abnormalities in tumours that superficially seem distinct, and mutations that are confined to specific tumours.

- The findings will guide the development of prognostic, diagnostic and therapeutic strategies.

Order from disorder sprung

ALAN ASHWORTH

During the past few years, the advent of hugely powerful DNA-sequencing technologies has delivered unprecedented insight into the nature of cancer genomes³. Hundreds of examples of genomes from several cancer types have already been produced, and this process will continue so that a definitive overview of cancer genomics can eventually be achieved. Nevertheless, it seems apposite to take stock of the themes that are emerging from comparisons of the genomes of different tumour types^{2,4} — studies that are giving us a fascinating first peek at the common mutational events and processes that shape cancer genomes.

The first impression that emerges from these comparisons is of the tremendous variation. Some types of cancer have, on average, relatively few genetic changes, whereas others show extraordinary mutational complexity. It is likely that most mutations in cancer genomes represent collateral damage that is unrelated to pathogenesis, but studies seeking candidates for driver mutations — those that contribute to the disease state⁵ — are revealing that both the number and nature of these candidates also differ considerably between cancers³. In some cases, we are seeing distinct cancer types with alterations in the same

cellular pathway brought about through driver mutations in different genes.

Mutual exclusivity of mutations in genes or pathways is also becoming apparent^{2,3}, providing clues as to which genes or pathways have non-redundant roles in oncogenesis. Using such data, we may eventually be able to understand the totality of biological perturbations that, acting together, result in the phenotypic diversity of human cancer. There is also the potential to deconvolve the order in which pathways are altered during disease progression, which is likely to be non-random owing to genetic interactions⁶. Gaining understanding of these two issues may be key to successful prevention and treatment strategies.

Comparing the type and frequency of genetic alterations, and the overall genomic structure, in different tumour classes also gives insight into the underlying mutational processes at play⁴. The accumulation of mutagenic cellular processes, endogenous and environmental exposures, and DNA-repair defects over many years or decades results in genomic 'scars'⁷ that can help us to understand the cause of the disease in an individual. The mutagenic fingerprints of tobacco smoking and sunlight exposure, for example, are obviously manifest in some cancers, but new phenomena are also being described and neologisms coined to describe them, such as chromothripsis for the shattering of individual chromosomes⁸ or kataegis for discrete genomic regions peppered with mutations⁹. Many other previously unknown mutational processes also seem to be involved in the development of

particular cancers. Studying these may reveal other influences on cancer development⁴.

An enormous amount has already been gleaned from these initial analyses, but much remains to be done. First, there is a strong case for completing a comprehensive and detailed survey of the entire panoply of human cancers. Paradoxically, rather than increasing complexity, this should allow further common themes to emerge from the noise. Second, most analyses of driver mutations have focused on protein-coding regions, which comprise only about 1% of the human genome. But it seems probable that studying non-coding regions will reveal a wealth of cancer-related mutations. Third, epigenetic alterations to the genome — which affect gene expression without changing the underlying DNA sequence — that cause or occur during cancer development need to be integrated into this landscape. Fourth, most of the tumours studied so far have been primary cancers before treatment; metastatic and treatment-resistant genomes also need to be studied in detail. Last, several studies have highlighted the genetic variation between individual cells within a tumour, and further analysis is needed to ascertain the prevalence of this phenomenon.

Alan Ashworth is at the Institute of Cancer Research, London SW7 3RP, UK.
e-mail: alan.ashworth@icr.ac.uk

A clinical perspective

THOMAS J. HUDSON

Classifying cancers using a broad, cross-tumour perspective provides not only biological insight, but also clinically relevant information. The value of the pan-cancer approach is demonstrated by Kandoth and colleagues' study² focusing on the simplest forms of mutation — single-nucleotide substitutions, or insertions or deletions of a few nucleotides, in the sequences of protein-coding genes. By

Figure 1 | Pan-cancer analysis. The Cancer Genome Atlas Research Network has presented a series¹ of initial findings from comparisons of the tumour characteristics and clinical data of thousands of patients, covering 12 major types of cancer.

applying stringent statistical tests based on the recurrence rates of such mutations, the authors identify 127 genes that are significantly mutated in a combined analysis of 3,281 tumours representing 12 tumour types. Although many genes in the list have previously been reported as mutated in cancer, the occurrence of these mutations across a wide range of cancers has not been appreciated until now.

Kandoth *et al.* also investigated these 127 genes as indicators of disease prognosis, using clinical data collected by the TCGA¹⁰, such as time to disease recurrence and time to death. Although survival analyses across cancer types are made difficult by the heterogeneity of clinical features related to different tumours, such as age of presentation, treatment modalities or metastatic potential, the large size of the study gave sufficient power to reveal several prognostic correlates. For example, mutations in several genes, including *BAP1*, *DNMT3A*, *KDM5C*, *FBXW7* and *TP53*, were found to correlate with poor prognosis, whereas mutations in two genes, *BRCA2* and *IDH1*, often correlated with improved prognosis.

It is worth noting that multi-tumour analyses can miss biomarkers that are prognostic indicators in single tumour types (such as *KDM6A* and *ARID1A* in bladder cancer), affirming the value of analysing data at both the individual tissue-type and pan-cancer levels. However, if the prognostic significance of pan-cancer genes is validated in large prospective studies of patients with cancer, clinical assessments of these genes may help to identify patients at higher risk of metastatic relapse, who could benefit from adjuvant therapies. This strategy has already been applied in patients with early-onset breast cancer through the use of multi-gene expression profiles^{11,12}.

In future, it will be useful to correlate genes identified as being relevant to multiple cancer types with drug responses, although this information will require greater integration of genomic profiles in clinical trials and cancer registries¹³, and new models of data sharing among research institutions¹⁴.

How can this pan-cancer project be exploited in drug development? One way is through the ranking of drug targets, which can be used to prioritize drug-development projects. More important, however, is the identification of functional relationships between groups of genes, or pathways. Pharmacological modulation of such pathways provides an alternative route for drug development when candidate genes encode proteins that are not deemed to be appropriate drug targets. Several

pathways implicated recently by other cancer-genome projects (such as pathways involved in RNA splicing, transcription regulation and metabolism) have been confirmed in the pan-cancer analysis, reinforcing the idea that these pathways should be considered as therapeutic targets.

We should anticipate many more surprises as additional tumour types¹⁵, mutation categories (including those in non-coding regions of the genome) and functional annotations of genomes¹⁶ are integrated in the next generation of pan-cancer studies. The determination of the common denominators — and the outliers — in cancer has the potential to benefit patients through improved laboratory tests, new drug-development opportunities and better-informed treatment decisions. ■

Thomas J. Hudson is at the Ontario Institute for Cancer Research, Toronto, Ontario M5G 0A3, Canada.

e-mail: tom.hudson@oicr.on.ca

1. www.nature.com/ng/focus/tcga/index.html
2. Kandoth, C. *et al.* *Nature* **502**, 333–339 (2013).
3. Garraway, L. A. & Lander, E. S. *Cell* **153**, 17–37 (2013).
4. Alexandrov, L. B. *et al.* *Nature* **500**, 415–421 (2013).
5. Lawrence, M. S. *et al.* *Nature* **499**, 214–218 (2013).
6. Ashworth, A., Lord, C. J. & Reis-Filho, J. S. *Cell* **145**, 30–38 (2011).
7. Lord, C. J. & Ashworth, A. *Nature* **481**, 287–294 (2012).
8. Stephens, P. J. *et al.* *Cell* **144**, 27–40 (2011).
9. Nik-Zainal, S. *et al.* *Cell* **149**, 979–993 (2012).
10. The Cancer Genome Atlas Research Network *Nature Genet.* **45**, 1113–1120 (2013).
11. Glas, A. M. *et al.* *BMC Genomics* **7**, 278 (2006).
12. Paik, S. *et al.* *N. Engl. J. Med.* **351**, 2817–2826 (2004).
13. Dancsey, J. E., Bedard, P. L., Onetto, N. & Hudson, T. J. *Cell* **148**, 409–420 (2012).
14. Check Hayden, E. *Nature* **498**, 16–17 (2013).
15. The International Cancer Genome Consortium *Nature* **464**, 993–998 (2010).
16. The ENCODE Project Consortium *Nature* **489**, 57–74 (2012).

PHYSICAL CHEMISTRY

Combs for molecules

Lasers known as frequency combs have been used to generate molecular spectra from samples within microseconds and with high spatial resolution. This offers fresh prospects for making microscopy observations in real time. SEE LETTER P.355

YARON SILBERBERG

Imagine a microscope that can be tuned to see specific molecules, or to analyse the molecular content of a sample. This dream has driven much of the work in advanced microscopy in recent years, particularly towards instruments that can be tuned to detect molecules through their specific vibration frequencies^{1–3}. In this issue, Ideguchi *et al.*⁴

report a crucial step in this direction: a microscopy method that uses light sources known as frequency combs. The work resolves a problem that has hindered the use of a technique called impulsive Raman spectroscopy in microscopy.

Molecules can be thought of as atoms connected by springs, and so their vibrations depend on their precise structure. This means that each molecule is characterized by a specific set of vibration frequencies, which