Lung cancer and melanoma laid bare: First comprehensive analysis of two cancer genomes

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Research teams led by the Wellcome Trust Sanger Institute announce the first comprehensive analyses of cancer genomes. All cancers are caused by mutations in the DNA of cancer cells which are acquired during a person's lifetime. The studies, of a malignant melanoma and a lung cancer, reveal for the first time essentially all the mutations in the genomes of two cancers.

Lung cancer causes around one million deaths worldwide each year: almost all are associated with smoking. The number of mutations found suggest that a typical smoker would acquire one mutation for every 15 cigarettes smoked.

Although malignant melanoma comprises only 3% of skin cancer cases, it is the cause of three out of four skin cancer deaths. The melanoma genome contained more than 30,000 mutations that carried a record of how and when they occurred during the patient's life.

"These are the two main cancers in the developed world for which we know the primary exposure," explains Professor Mike Stratton, from the Cancer Genome Project at the Wellcome Trust Sanger Institute. "For lung cancer, it is cigarette smoke and for malignant melanoma it is exposure to sunlight. With these genome sequences, we have been able to explore deep into the past of each tumour, uncovering with remarkable clarity the imprints of these environmental mutagens on

DNA, which occurred years before the tumour became apparent.

"We can also see the desperate attempts of our genome to defend itself against the damage wreaked by the chemicals in cigarette smoke or the damage from ultraviolet radiation. Our cells fight back furiously to repair the damage, but frequently lose that fight."

The studies used powerful new DNA sequencing technologies to decode completely the genome of both tumour tissue and normal tissue from a lung cancer and a malignant melanoma patient. By comparing the genome sequence from the cancer to the genome from healthy tissue they could pick up the changes specific to the cancer. The studies are the first to produce comprehensive genome-wide descriptions of all classes of mutation, producing rich accounts of the genetic changes in the development of the two cancers.

"In the melanoma sample, we can see sunlight's signature writ large in the genome," says Dr Andy Futreal, from the Wellcome Trust Sanger Institute. "However, with both samples, because we have produced essentially complete catalogues, we can see other, more mysterious processes acting on the DNA. Indeed, somewhere amongst the mutations we have found lurk those that drive the cells to become cancerous. Tracking them down will be our major challenge for the next few years."

The lung cancer genome contained more than 23,000 mutations, the melanoma more than 33,000. Identifying the causative mutations among the large number found poses a challenge, but the complete genome sequences mean, that for the first time, that challenge can be met.

"Nearly ten years on, we are still reaping the benefit from the first human genome sequence and we have much still to do to get to grips with these new disrupted landscapes of cancer genomes," explains Dr Peter Campbell from the Wellcome Trust Sanger Institute. "But the

knowledge we extract over the next few years will have major implications for treatment. By identifying all the cancer genes we will be able to develop new drugs that target the specific mutated genes and work out which patients will benefit from these novel treatments."

A complete genome catalogue for each patient would be expected to help select between treatments and to direct treatment in the most efficient and cost-effective way. The Sanger Institute is already working with researchers at Massachusetts General Hospital on a large scale project to tie genetic changes in cancers to their responses to anticancer treatments.

"We want to drive healthcare through better understanding of the biology of disease," says Sir Mark Walport, Director of the Wellcome Trust. "Previous outcomes from our Cancer Genome Project are already being fed into clinical trials, and these remarkable new studies further emphasise the extraordinary scientific insights and benefits for patients that accrue from studying the genome of cancer cells.

"This is the first glimpse of the future of cancer medicine, not only in the laboratory, but eventually in the clinic. The findings from today will feed into knowledge, methods and practice in patient care."

The human genome is large. Moreover, there are more than one hundred different types of cancer and sequencing genomes is expensive. To ensure that thousands of cancers ultimately are sequenced in the same way as these two, the International Cancer Genome Consortium has been established, on the model of the Human Genome project itself to coordinate cancer genome sequencing across the globe.

These catalogues of mutations across the broad diversity of cancer types will provide powerful insights into the biology of cancer and will be the foundation for understanding cancer causation and improving

prevention, detection and treatment.

One mutation every day

Ravages in a lung cancer genome

Research published in *Nature* shows that the genome of a lung cancer patient has more than 20,000 mutations: this total implies that a typical smoker would acquire one mutation for every 15 cigarettes smoked. The cancer genome is ravaged by mutations, many of which are repaired as the genome tries to defend itself.

In many cases, that battle is lost and some of the many thousands of mutations hit key genes and lead to cancer.

In the study, the researchers compared the genomes in normal blood cells and tumour cells from a patient with small cell lung cancer (SCLC). They sequenced the genome a total of 60 times over to develop a comprehensive catalogue of all known types of DNA mutation.

"For the first time, we have a comprehensive map of all mutations in a cancer cell," said Dr Peter Campbell, senior author on the work, from the Cancer Genome Project at the Wellcome Trust Sanger Institute, "The profile of mutations we observed is exactly that expected from tobacco, suggesting that the majority of the 23,000 we found are caused by the cocktail of chemicals found in cigarettes. On the basis of average estimates, we can say that one mutation is fixed in the genome for every 15 cigarettes smoked."

The mutations range from single-letter changes in the code to deletions or rearrangements of hundreds of thousand of letters. Most are 'passenger' mutations, previously defined by the team as mutations that do not influence the development of the cancer, but are a consequence

of the highly mutagenic environment in many cancer cells.

"Cancers occur when control of cell behaviour is lost - cells grow how, when and where they shouldn't," explains Dr Andy Futreal from the Wellcome Trust Sanger Institute. "Mutations in DNA caused by, for example, cigarette smoke are passed on to every subsequent generation of daughter cells, a permanent record of the damage done. Like an archaeologist, we can begin to reconstruct the history of the cancer clone - revealing a record of past exposure and accumulated damage in the genome."

The study was so comprehensive that the team could see signatures of an undiscovered system of DNA repair, reducing the mutations in highly active genes, suggesting the genome seeks to preserve these regions above many others.

However, as previous studies suggested, there was not one mutation that stood out as 'the lung cancer gene'. One gene - CHD7 - was found to be mutated in several SCLC samples. This gene is part of an emerging pattern that cancers often contain mutations in genes that are generalists in regulating genetic activity alongside more specific changes.

This work and the companion study on malignant melanoma using massively parallel sequencing portend an era in which the forces of mutagens shaping our genome can be described and the consequences of these processes can be decoded.

It is clear that rates of lung cancer fall to around normal some 15 years after quitting smoking: the suspicion is that lung cells containing mutations are replaced by new cells derived from lung stem cells that are clear of mutation.

"This is a difficult disease to diagnose and treat," continues Professor

Stratton, "but fortunately we do know how people can minimize their risk of lung cancer. Even current smokers substantially reduce their risk by giving up now - the more time passes off tobacco, the more the risk decreases."

Signatures of sunlight

Malignant melanoma genome contains 33,000 mutations

In a landmark study, researchers have described the first comprehensive catalogue of somatic mutations in a cancer genome. The breadth and clarity of the view of the genome from a patient with malignant melanoma is matched only by a companion study on lung cancer, published in the same issue of *Nature*.

The melanoma genome contains more than 33,000 mutations, many of which bear the imprint of the most common cause of melanoma - exposure to ultraviolet (UV) light. But the comprehensive catalogue of mutation reveals other more unusual mutations and many not related to exposure to UV light.

Malignant melanoma is responsible for three out of four skin cancer deaths: most forms of skin cancer are relatively treatable, especially if detected early.

"This is an unprecedented view of a cancer genome," says Professor Michael Stratton, from the Cancer Genome Project at the Wellcome Trust Sanger Institute. "Written within this code is the history of this cancer - its mutations from UV light and the mutations it acquired when it spread within the patient. We have revealed the archaeology of exposure in this cancer genome, which becomes a palimpsest of successive mutations."

"It is amazing what you can see in these genomes," comments Dr Peter Campbell from the Wellcome Trust Sanger Institute. "UV-light-induced mutations leave a typical signature, forming the vast majority of the mutations.

"Indeed because of the clarity of the genome data, we can distinguish some of the early, UV-induced mutations from the later mutations that do not have this signature, presumably occurring after the cancer cells spread from the skin to deeper tissues.

The sequence also shows the genome's attempts to protect itself from damage, with DNA repair systems most active in gene regions, whereas the regions between genes are left less well guarded. Even with these actions, 182 changes in genes that would impair their function were charted.

"Within the lists of disrupted genes are all those that have driven the original cell to this malignant state," comments Dr Andy Futreal, from the Cancer Genome Project at the Wellcome Trust Sanger Institute. "We know that this cancer sample has a mutation in BRAF and other genes already implicated in melanoma. To discern all the important changes, we will need to analyse more samples."

The genomes - cancer cell and normal cell - were sequenced more than 70 times over to produce accurate data.

The project was led by researchers from the Wellcome Trust Sanger Institute. In 2002, this group discovered that a mutation in one gene called BRAF was important in driving development of melanoma. That discovery has already driven the development of novel therapies that are in clinical trials.

More information: Pleasance ED et al. (2009) A small-cell lung

cancer genome with complex signatures of tobacco exposure. *Nature* doi:10.1038/nature08629
Pleasance ED, Cheetham RK et al. (2009) A comprehensivdoi:10.1038/nature08658mutations from a human cancer genome. Nature doi:10.1038/nature08658