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Beyond the genome

Studies of the epigenomic signatures of many healthy and diseased human tissues could provide crucial information to link genetic variation and disease.

The Greek prefix *epi-* can signify upon, on, over, near, at, before, and after. Most of those could apply to its use in the term 'epigenetics' — particularly the last of them. It is some 14 years, almost to the day, that *Nature* published the draft sequence of the human genome. Now, in this issue, we publish results from a subsequent study on the non-genetic modifications to the genome — epigenetic modifications — that crucially determine which genes are expressed by which cell type, and when.

It is hard to think of any branch of human biology that has not benefited from the human genome sequence. Its legacy has perhaps been most notable in advances in our appreciation of the part that genetics and genetic variation play in the normal functioning of a human body and in disease. But despite the progress, each question that the genome helps to answer throws up further questions. Much remains to be understood about how genetic information is interpreted by the individual cells in our body.

This is where epigenetics comes in. Upon the genome, on the genome, over the genome — take your pick — epigenetics collectively describes changes in the regulation of gene expression that can be passed on to a cell's progeny but are not due to changes to the nucleotide sequence of the gene.

Soon after the human genome sequence had been completed, it became clear that an epigenome — a map of the genome-wide modifications made to DNA and the protein scaffold that supports it — would also be required. The task at hand was, as researchers like to say, not trivial. Every cell in the body carries the same genome (with a few exceptions), but the epigenome changes with cell and tissue type.

Epigenetics is still an emerging science, but researchers are now building tools to study epigenetic changes in the genome in a systematic and genome-wide way. In 2012, *Nature* celebrated the publication of the results of the ENCODE project, the aim of which was to describe all the functional elements encoded in the human genome by mapping epigenetic modifications (see nature.com/encode).

ENCODE was a pioneer in scale of effort and development of specialized analytical software, and has already had a tremendous impact on human-genetics studies. But its clinical application is limited because most of its results come from a small number of laboratory cell lines. Clinically useful epigenetic information must instead be drawn directly from all the different cell types that make up the human body.

This type of epigenomic information has now been gathered, in the Roadmap Epigenomics Project directed by the US National Institutes of Health. This project set out to generate and publicly share epigenomic data from stem cells, from mature cells from a variety of different tissues from healthy people, and from patients with diseases such as cancer, and neurodegenerative and autoimmune disease.

The main results of this vast project are published in this issue starting on page 313, as well as in several other Nature Publishing Group journals.

Insights into three fundamental aspects of epigenetics emerge: how the epigenome affects gene expression; how the epigenome changes during stem-cell differentiation (that is, during normal development); and how it changes during disease.

The results emphasize the central role of epigenomic information in understanding these processes. Crucially, what emerges is that it is not just one or two types of modification that matter. Biology is rarely that simple. Instead, combinations of modifications predict gene activity in ways that a single type of modification does not.

"Tackling disease using information on the genome alone has been like trying to work with one hand tied behind the back."

A causal link between epigenetic changes and disease has so far been hard to establish. Identifying such changes is necessary, however, if we are to understand the underlying disease mechanism and design targeted treatments. With the new wealth of data, consistent alteration in the epigenetic landscape could identify candidate genes and pathways for further follow-up. And time-course studies of the epigenetics of cell types relevant to a specific disease could indicate whether epigenetic changes have a role in disease progression, or only in its onset.

One reason that it has been difficult to relate some diseases to disruption in DNA function is that many of the key changes occur in poorly understood regions of the genome, usually outside those parts that code for proteins. Epigenomic maps such as those published today should help scientists to navigate this poorly charted landscape. By overlaying these maps, made in relevant cell types, researchers can determine, for example, whether an epigenetic change associated with a given disease lies in a region of the genome that regulates gene activity. If it does, then this overlap provides a possible lead to be explored.

Cancer is often called the disease of the genome, but the genome does not exist, or operate, in splendid isolation. Of all diseases, cancer has been linked most unambiguously to epigenetic aberrations. Scientists have long suspected that epigenomic organization affects the genomic location of the mutations that provoke cancer. The new findings suggest that this is true, and they go further. They show that the epigenome of a cancer cell carries a fingerprint of the cell type that originated the cancer. This is crucial information, especially for cancers in complex tissues such as the liver, which cannot presently be traced to their original cell type.

In human diseases, the genome and epigenome operate together. Tackling disease using information on the genome alone has been like trying to work with one hand tied behind the back. The new trove of epigenomic data frees the other hand. It will not provide all the answers. But it could help researchers decide which questions to ask. ■