Computation to unravel how genes are regulated and shed light on how cells become different

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A closer alliance between computational and experimental researchers is needed to make progress towards one of biology's most challenging goals, understanding how epigenetic marks contribute to regulation of gene expression. This emerged from a recent workshop organised by the European Science Foundation (ESF), "Computational Approaches to the Role of Epigenetic Marks in Transcription Regulation".

Epigenetics studies features of the DNA and chromatin that are stably inherited through cell division but that are beyond the DNA sequence itself. It has been well established that epigenetic features influence the transcription process whereby the DNA sequences of genes are translated into the RNA and protein products that determine structure and function. Just as crucially, it is believed that epigenetics also allows changes to these gene expression patterns to be remembered, so that different organs and tissues can emerge during embryonic development, and retain their identity and function for the rest of the organism's lifetime.

Changes in gene expression can result from modifying chromatin, which is the structure comprising proteins and DNA that is the repository for genetic information. Marks are imposed that serve as templates for modification of the chromatin, altering the ability of genes to be accessed by the DNA transcription machinery. The result is that some genes are suppressed and others are silenced altogether. One of the key

questions discussed at the ESF workshop concerned how these changes are “remembered” during cell division through replication of the epigenetic marks, and yet how in some cases these can be reversed, allowing a cell to be reprogrammed so that it can take on a different role or function.

The ability of cells to be reprogrammed by having epigenetic marks removed is of great interest and importance in stem cell research, said Erik van Nimwegen from University of Basel in Switzerland, convenor of the ESF workshop. In some cases cells can be “de-differentiated” in this way, losing their normal function and becoming stem cells again, capable of subsequently dividing into different cell types by acquiring once again appropriate controls over expression of their genes.

The ability to lose as well as gain epigenetic marks that constrain the expression of certain genes is also important in early embryonic development, when rapid changes in structure and function are occurring. One presentation at the workshop by Dirk Schübeler of the Friedrich Miescher Institute in Basel described how whole sets of genes can have their expression modified just temporarily through the process of DNA methylation, one of the main mechanisms for blocking access to the underlying DNA of a gene.

But with so much still to be discovered about the complex and subtle nature of gene regulation through epigenetic modification, the greatest triumph of the ESF workshop lay not so much in the individual presentations, but the collective decisions over future research priorities, and the relationships established between computational and experimental biologists.

“We think that the discussions among experimentalists and theorists regarding interesting outstanding questions has shaped the planning for future research of all participants,” said van Nimwegen. “Several

participants felt the workshop was rather unique in that it brought together a wide variety of researchers working in a field that is rather new."

Experiments and observation provide the data about gene expression patterns, while computational methods analyse the changes over time and help identify sequences that have been in effect memorised, and others that have been "forgotten". This phenomenon whereby cells in effect remember what has happened to them and respond through changes in their expression is fundamental to development of organisms, along with their structure and function during their lifetime, as well as inheritance of adaptations to environmental factors.

Source: European Science Foundation