LEARNING HOW CHROMATIN LOOPS THE LOOP

Background

When DNA is complexed with proteins and compacted into chromosomes it is known as chromatin. Changes in the physical arrangement of chromatin appear to have a functional role in the nucleus; in particular, there is increasing evidence that signal-mediated changes in chromatin structure govern gene expression.

Often, these structural changes involve the looping of chromatin, which can bring spatially distinct regions of DNA into close contact with one another and with proteins in the nucleus. This can lead to the activation or repression of gene expression.

The structural changes are mediated by specialised sequences in DNA called matrix attachment regions (MARs), which, as their name suggests, interact with the nuclear matrix (or the nuclear skeleton). The molecular processes that trigger these changes in chromatin organisation are poorly defined.

Advance

Indian Senior Research Fellow Sanjeev Galande, based at the National Centre for Cell Science, Pune, India, has been exploring how changes in chromatin assembly can affect gene expression. His team is particularly interested in MARs and the proteins that bind them.

Dr Galande's team is using the process of T-cell activation and differentiation as a model system to explore the molecular processes behind changes in chromatin architecture and gene expression. Specifically, the researchers are studying a T-cell-specific protein called Special AT-rich DNA-binding protein 1 (SATB1), which has been shown to bind MARs (causing chromatin to form loops) and to suppress gene expression.

The researchers found that SATB1 binds a protein called PML. This protein is an important component of a nuclear substructure called the promyelocytic leukaemia (PML) body, the function of which is unclear.

The direct interaction between PML and SATB1 forces a gene-rich region of DNA (called MHC-I) into a distinct series of chromatin loops by tethering MARs to the nuclear matrix. Dr Galande's group demonstrated that the loop configuration dynamically changes upon external stimulus, and through such signal-dependent changes, the SATB1–PML complex regulates gene expression.

To build on this work, the researchers are now exploring the role of a PDZ-like domain in SATB1. PDZ domains are involved in signal transduction, so the researchers hypothesise that SATB1 acts as a link between PDZ-mediated signalling and changes in chromatin architecture. So far they have shown that the phosphorylation status of the PDZ-like domain of SATB1 dictates its ability to turn genes on or off. Phosphorylation plays a vital role in cell signalling systems.

Wellcome Trust grant

Indian senior research fellowship; 'PDZ domain-mediated signalling in the nucleus: Role of SATB1 in the regulation of global gene expression via alterations in chromatin organization.' 2004

How it's making a difference

Many cancers arise because the controlling pathways of the cell cycle have been disrupted. Structural changes to chromatin, called chromatin remodelling, play an essential role in many of these cell cycle 'checkpoints'. Dr Galande and colleagues have developed a number of assays for screening these structural changes under different conditions.

This research is in its early stages, but development of this kind of assay has the potential for use in cancer screening, by allowing researchers to identify changes in chromatin structure that are known to be associated with particular cancers.

Dr Galande's team has also developed a novel system to express and purify proteins, which can produce highly purified, tag-free proteins in a shorter time than many systems currently in use.

In 2007 Dr Galande received the Indian National Bioscience Award for Career Development.

References

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