How 'molecular machines' kick start gene activation revealed

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How 'molecular machines' inside cells swing into action to activate genes at different times in a cell's life is revealed today in new research published in *Molecular Cell.*

Genes are made of double stranded DNA molecules containing the coded information an organism's cells need to produce proteins. The DNA double strands need to be 'melted out' and separated in order for the code to be accessed. Once accessed, the genetic codes are converted to messenger RNAs (mRNA) which are used to make proteins. Cells need to produce particular proteins at different times in their lives, to help them respond and adapt to changes in their environment.

The new study outlines exactly how a molecular machine called RNA polymerase, which reads the DNA code and synthesizes mRNA, is kickstarted by specialised activator proteins. The scientists have discovered that RNA polymerase uses a tightly regulated internal blocking system that prevents genes from being activated when they are not needed.

Using electron microscopy to look at the inner workings of bacterial cells, the researchers discovered that the DNA strand-separating process is kickstarted when RNA polymerase is modified by an activator protein, which the cell sends to the site of the gene that needs to be switched on.

This activator protein jump-starts the RNA polymerase machine by removing a plug which blocks the DNA's entrance to the machine. The

activator protein also causes the DNA strands to shift position so that the DNA lines up with the entrance to the RNA polymerase. Once these two movements have occurred and the DNA strands are in position, the RNA polymerase machine gets to work melting them out, so that the information they contain can be processed to produce mRNA, and ultimately allow production of proteins.

Professor Xiaodong Zhang, lead author of the paper from the Department of Life Sciences at Imperial College London, explains the significance of the team's findings, saying:

"Understanding how the RNA polymerase gene transcription 'machine' is activated, and how it is stalled from working when it is not needed, gives us a better insight than ever before into the inner workings of cells, and the complex processes that occur to facilitate the carefully regulated production of proteins."

Professor Martin Buck, Head of Imperial's Division of Biology and one of the paper's co-authors, adds that understanding how this process works in bacteria cells is of particular interest, because it is this gene transcription and protein production process which allows bacterial cells to adapt, respond and thrive despite changes in their environment:

"In other words, this is the process that occurs inside bacteria that makes them so good at survival. Many bacteria cause infection and disease in humans, and are hard to defeat. Bacterial RNA polymerase is a proven target for antibiotics such as rifampicin, against which many bacteria have become resistant. Insights gained form our research will now provide opportunities and strategies for the design of novel antibacterial compounds," he concludes.

Source: Imperial College London