Our genes can be set on pause

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New evidence in embryonic stem cells shows that mammalian genes may all have a layer of control that acts essentially like the pause button on your DVR. The researchers say the results show that the pausing phenomenon, previously thought to be a peculiarity of particular genes, is actually a much more general feature of the genome.

The findings are reported in the April 30th issue of the journal *Cell*, a Cell Press publication.

"We're coming to the realization that we've been missing out on an entire second step in the control of gene expression," said Richard Young of the Whitehead Institute and Massachusetts Institute of Technology. "There's tremendous excitement," he said, and some healthy debate too.

Notably, Young's team has shown that the infamous cancer gene known as c-Myc plays a major role in the pause release of many genes throughout the genome. Their fundamentally important findings may therefore ultimately have practical application in the treatment of some of the nastiest cancers, according to the researchers.

For decades, scientists have known that transcription is controlled by the recruitment of DNA binding factors to promoters, where they act as a kind of molecular Velcro for the polymerase enzymes that copy DNA into the mRNA templates for proteins, Young explains. "We still believe that's true," he said. "The surprise is that's only the first step."

They've now shown that other players cause the recruited polymerases to

freeze in their places - in effect pausing gene activity. It is the job of still other transcription factors to act as a pause release.

As evidence for the importance of the pausing function, a genome-wide analysis of embryonic stem cells showed that the bulk of polymerases can be found adjacent to promoters at any given time, even when the genes in question are some of the most actively transcribed. Pause factors (known as DSIF and NELF) are usually there too, consistent with the notion that they bind the enzyme after it has only just gotten started transcribing the DNA. The interactions of still other players, including one that is recruited by the transcription factor c-Myc, must then release the pausing for the genes to come back 'on'.

Young said he initially thought the pausing process might be fairly unique to embryonic stem cells, but he doesn't think so any more. When they began the study, they also expected the embryonic cells would show this sort of pausing at select developmental genes only. Instead, they found that polymerase was paused at about 75 percent of all promoters.

"We found it was occurring everywhere - at all genes," Young said. "The polymerases come for a visit and then they pile up downstream of the promoter." They make only a very small stretch of RNA before they stop, awaiting the signal to continue. Some of the paused polymerases appear to remain in their suspended state indefinitely, he says.

Young said he thinks this second layer of control likely offers cells some added flexibility. In some cases, he notes, this sort of pausing seems to allow a rapid response to particular cues. The pause function might also be necessary, he says, because polymerases can be surprisingly sloppy in doing their jobs. The enzymes will often transcribe in two directions, one of them clearly backwards.

"It's a little clueless," Young said. "Pause control may be a way of

ensuring that transcription continues only in the correct direction, and at real genes instead of willy-nilly."

Although Young is not an expert in cancer, he says that the connection of this pausing process to c-Myc could make some waves.

"Myc is so important in cancer," he says, noting that Myc is implicated in at least 15 percent of human cancers including some of those that are the toughest to get rid of and that tend to come back. There is some evidence in mice that shutting Myc down can lead cancer cells to shrivel up and die, but Myc itself isn't an ideal drug target.

"Now we know what Myc does and we know the kinase it recruits," Young said. That's key because kinases often do make good drug targets.

The new findings therefore offer new insight into how Myc works and a new rationale and strategy for trying to shut it down as a way to treat cancer. Young said there is surely a lot more to learn about pause control and its release too, with potentially other implications for human disease.

More information: Peter B. Rahl et al, "c-Myc regulates transcriptional pause release" Cell, April 30, 2010. DOI:10.1016/j.cell.2010.03.030

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