RNA interference plays bigger role than previously thought

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In a paper published today online in the journal *Nature,* IBM and the Genome Institute of Singapore (GIS) reported findings from a joint research study that provides new information on how stem cell differentiation is controlled by microRNAs.

The two teams have shown that microRNAs -- small molecules that are an important regulatory component in the machinery of living cells -- have roles that go well beyond what was previously thought.

In 2006, IBM scientists developed a mathematical model that led to a conjecture about an expanded role for microRNAs. The team decided to test the hypothesis by focusing on mouse stem cells. IBM used computation to guide the experimental effort that GIS carried out.

The work is expected to provide new insights on stem cell differentiation as well as on the role of microRNAs in cell process regulation and the onset of cancer, neurodegenerative disorders, diabetes and other diseases. The research is also expected to suggest future avenues for novel diagnostics and the development of therapeutics.

"We have made yet another step towards understanding the intricate nature of microRNAs and the roles they play in the regulation of cellular processes," said Isidore Rigoutsos, manager of the Bioinformatics Group in IBM Research's Computational Biology Center. "The finding that microRNAs can extensively target locations in the amino acid coding regions of a transcript is an exciting discovery and reveals another

important aspect of microRNA activity."

GIS Senior Group Leader Bing Lim added, "We learn from this study that the targeting of coding regions by microRNAs can also have a real impact on cells. We observed that a single microRNA forced into the powerful embryonic stem cell can impose differentiation. This is exciting because one could envisage using microRNAs as a small molecule to control the differentiation of stem cells, or to make new stem cells. The fun part of this research was the visualization of a trend of thought from computational prediction all the way to cell transformation."

Details of discovery:

For more than a decade, microRNAs were assumed to interact primarily with their targets through the 3' untranslated region (3'UTR) of the targets' mRNA. The nucleotide sequences of the targeted locations were believed to be generally conserved across different organisms whereas interactions with mRNA regions beyond the 3'UTR were thought to be atypical.

Some of the new research findings suggest that microRNA targets in the amino acid coding region (CDS) of a gene's mRNA may in fact be as frequent as those in the mRNA's 3'UTR, providing experimental evidence to a conjecture put forth in an earlier publication by the two teams. It also shows that a gene's CDS serves as template of microRNA targeting activity, in addition to its coding for the corresponding protein's amino acid sequence.

Working with three microRNAs whose expression increases upon differentiation of mouse embryonic stem cells (ESCs), the teams showed that Nanog, Oct4 and Sox2, three transcription factors that are central to maintaining the pluripotency of mouse ESCs and determining the

initiation of differentiation, are controlled through their CDS region by the three studied microRNAs. By introducing mutations at the identified target locations, the two teams showed that they could prevent the down-regulation of these transcription factors and delay stem cell differentiation.

For the majority of the validated microRNA targets, their sequence is not conserved in the rhesus monkey and mouse counterparts of Nanog, Oct4 and Sox2. This suggests that seeking putative microRNA targets by aligning the instances of a gene across different organisms will underestimate the number of bona fide microRNA targets.

Additionally, the studied microRNAs generally have multiple targets in the CDS region of the same gene possibly suggesting an underlying need for redundancy that can ensure the downregulation of the intended target.

Finally, several of the studied targets stride exon-exon junctions: this finding suggests that microRNAs play a role in the selective targeting of a gene's splice variants.

"This discovery has vast implications for the role that computational models can play in biological science," said Ajay Royyuru, senior manager for the Computational Biology Center at IBM Research. "Computational biology allows scientists to develop theories using powerful computers and even preliminarily prove those theories prior to conducting experiments in wet labs – which reduces the time spent on trial and error throughout the process of scientific discovery."

GIS Executive Director Edison Liu said, "This work is a great example of how future medical discovery will progressively require the joint efforts of computer scientists working in conjunction with biologists. The complexity of the control of human cells through regulatory

networks demands computational modeling in order to decipher the signals from the noise. But in the end, it still boils down to doing the lab experiment."

Citation: The report on this work, "MiRNAs to Nanog, Oct4 and Sox2 coding regions modulate embryonic stem cell differentiation," by I. Rigoutsos of IBM T.J. Watson Research Center, Yorktown Heights, NY, and, Y. Tay, J. Zhang, A. Thomson, and B. Lim of the Genome Institute of Singapore, is published online in the Sept. 2008 issue of the journal *Nature.*

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