PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Epigenetic switch for Igf2

ArticleInfo		
ArticleID	:	4985
ArticleDOI	:	10.1186/gb-spotlight-20040728-01
ArticleCitationID	:	spotlight-20040728-01
ArticleSequenceNumber	:	48
ArticleCategory	:	Research news
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2004–7–28 OnlineDate : 2004–7–28
ArticleCopyright	:	BioMed Central Ltd2004
ArticleGrants	:	
ArticleContext	:	130595511

Cathy Holding
Email: cathyholding@aol.com

Chromatin loops form a simple epigenetic switch that regulates Igf2 expression, according to the authors of a letter in Nature Genetics this week. The mechanism could model epigenetic regulation of long-distance interactions for other imprinted genes in the genome (*Nat Genet* 2004, DOI:10.1038/ng1402).

Wolf Reik's group in the Laboratory of Developmental Genetics and Imprinting at the Babraham Institute, Cambridge, UK, felt "under pressure" to test and prove their prediction of a year ago that the differentially methylated regions (DMRs) in Igf2 and H19 come into physical contact and interact to allow the intervening DNA to loop out, Reik told us.

The authors tested the prediction with two different strategies. In the first, Reik's team used yeast Gal4 insertion technology to show that in maternal chromosomes, Gal4 links up with the H19 DMR and the DMR1 of Igf2, while on the paternal chromosome it links up with the H19 DMR and the DMR2 of Igf2. Secondly, chromosome capture conformation confirmed the identity of sequences held in close physical contact in the crosslinked loops.

But their interpretation of the data is not necessarily correct, according to Rolf Ohlsson at the Evolutionary Biology Centre at Uppsala University, Sweden. He commented that although Reik involves this higher-order chromatin conformation in his model, "we don't know - it could very well be that the H19 DMR interacting with [Igf2] DMR1 is implementing two other tasks: one is to delay replication timing and the other is to maintain methylation-free DMR1." The model looks fine on paper, but in three dimensions could be more problematic, Ohlsson said.

Michael P. Kladde, from the faculty of genetics at Texas A&M University, agreed. "For the maternal allele, it says to me that if everything can loop, what's to keep the H19 enhancer from looping back and hitting the Igf2 promoter?" But Kladde told us he thought there might be a suggestion that the chromatin is packaged up into a very tight loop so that even if the H19 enhancer does contact the Igf2 promoter, it would not be able to load the transcription machinery and fire it.

As another group trying to determine how the H19 gene is repressed and silenced on the paternal allele, the authors of an accompanying paper show that the two parental-specific roles of the H19 DMR - methylation maintenance and insulator assembly - are antagonistic. Marisa S. Bartolomei, at the Howard Hughes Medical Institute and University of Pennsylvania School of Medicine, introduced point mutations into four 21-bp repeats hypothesized to be required for maternal-specific blocking of the enhancer and for establishing and maintaining paternal methylation, eliminating nine of ten CpGs there.

Researchers previously believed that in germ cells, the epigenetic marking for gene expression was predetermined and stable and that it took a really radical disease state to disrupt that, Bartolomei said. Her work now shows this regulation to be very dynamic, and that subtle perturbations can cause deregulation, she said. "Methylation needs to be maintained in order to keep H19 and Igf2 expression properly regulated. If you have a slight physiological perturbation, you can disrupt regulation at the locus - which has great consequences for an embryo," Bartolomei said.

Neither Reik nor Bartolomei believed their results were linked, a conclusion that surprised Kladde. "To me it seems like [Bartolomei's paper] would be quite connected to the [Reik] paper - because the first experiment I would go do is I would use their 9C mutated allele and I would see if it changes the loops," said Kladde.

References

1. *Nature Genetics*, [http://www.nature.com/ng/]

2. Wolf Reik, [http://www.bi.bbsrc.ac.uk/research/developmental%20genetics/reik/index.htm]

3. Epigenetic modifications in an imprinting cluster are controlled by a hierarchy of DMRs suggesting long-range chromatin interactions

4. Evolutionary Biology Centre, Uppsala University, [http://www.ebc.uu.se/index_eng.htm]

5. Michael P. Kladde, [http://biochemistry.tamu.edu/subpages/sub_faculty/facpage.php3?name=1a_kladde]

6. Marisa S. Bartolomei, [http://www.hhmi.org/research/investigators/bartolomei_bio.html]