NUS National University of Singapore
Department of Biological Sciences
Faculty of Science

BIOLOGY COLLOQUIUM

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Hosted by A/P Ge Ruowen

Noncoding RNA Regulation of Myeloid Transcription Factors, DNA Methylation, and Leukemia

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Tight regulation of myeloid transcription factors PU.1 and C/EBPa is necessary for proper hematopoietic stem cell function and granulopoiesis, and dysregulation of these genes can lead to development of leukemia. We have focused on regulation of these two genes by noncoding RNAs (ncRNAs). In the case of PU.1, we previously described a long antisense RNA that is initiated from a discrete promoter in intron 3 and extends past the transcription start site. This transcript is expressed at highest levels in T cells, in which PU.1 is not expressed, and can inhibit PU.1 protein. siRNAs which target this antisense transcript can increase PU.1 mRNA and protein, and induce differentiation of leukemic cells. There is a second long noncoding RNA in the PU.1 locus, which is initiated in the upstream regulatory element (URE), and extends for greater than 10 kb toward the transcription start site. This transcript is entirely nuclear, and its function is unknown. We are in the process of testing the function of both transcripts by using BAC transgenics in which transcription terminators have been used to abrogate expression of the noncoding RNA.

In the case of C/EBP alpha, we identified a ncRNA extending beyond the polyadenylation signal of the C/EBPa gene. In contrast to PU.1, this extracoding transcript correlates positively with C/EBP alpha mRNA, and siRNA knockdown of the ncRNA leads to a decrease in C/EBP alpha mRNA and increase in methylation of the locus. Overexpression of this ncRNA leads to an increase in expression of C/EBP alpha in a cell line (K562) in which C/EBP alpha is methylated and not expressed.

In summary, we have initiated studies of long noncoding RNAs in both the PU.1 and C/EBP alpha genes. The function of these RNAs appears to be completely different. In the case of PU.1, an antisense noncoding RNA downregulates PU.1 expression. In the case of C/EBP alpha, an extracoding RNA inhibits methylation of the locus and increases mRNA levels.

Artwork by Ann Nee, DBS, NUS