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Novel Roles of Intragenic DNA Methylation in Transcription and Pre-mRNA Splicing

1-2 PM

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Alika K. Maunakea is the great-grandson of the late Kupuna Katherine Maunakea of the Waianae coast who introduced him to traditional Hawaiian medicine. Inspired by his Kupuna, Alika studied molecular and cell biology to investigate the pharmacological value of Hawaiian medicinal plants at Kamehameha Schools. After graduating in 1997, Alika went on to receive his bachelor's degree in Biology at Creighton University and Ph.D. in Biomedical Sciences at the University of California, San Francisco. Currently, he is a post-doctoral research fellow at the National Institutes of Health in Bethesda, Maryland working with Dr. Keji Zhao in the field of epigenetics within the National Heart, Lung & Blood Institute.

Abstract:

In mammals, DNA methylation is essential to embryonic development, differentiation, cell cycle control, and maintenance of genome stability. At promoters, methylation generally precludes transcription by blocking the binding of transcriptional activators directly or indirectly through the recruitment of methyl-binding proteins and co-repressor complexes containing histone deacetylases that cooperatively facilitates the formation of heterochromatin. However, recent genome-wide studies have revealed that DNA methylation within gene bodies is far more frequent than at promoters. Such intragenic methylation is evolutionarily conserved, implying that it has a common ancestral function. Using high-throughput methodologies coupled with in-depth investigation of specific loci, we have found that intragenic DNA methylation regulates alternate promoter activity in vitro and in vivo, offering a mechanism for the expression of alternate transcripts in a tissue and cell type-specific manner. In addition, preferential positioning of DNA methylation over exons compared with introns prompted speculation for its potential role in pre-mRNA splicing, which remains largely unsubstantiated. We found that intragenic DNA methylation operates in exon definition to modulate pre-mRNA splicing and can enhance exon recognition via recruitment of the methyl-binding protein MeCP2. Together, these studies provide novel insight into the functional roles of intragenic DNA methylation in transcription and pre-mRNA splicing with important implications to disease.