Does intragenic DNA methylation determine differential exon expression?

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Background

DNA methylation is an important epigenetic marker associated with the regulation of gene expression in eukaryotes. While promoter methylation is relatively well-characterized as a gene silencer in vertebrates, the role for intragenic methylation remains unclear. The genome-wide location of intragenic DNA methylation was determined in many eukaryotic species [1], along with analyses of messenger RNA. A recent study suggests that DNA methylation affects exon recognition and is influenced by the GC architecture of the exon and flanking introns [2]. In this study we investigate the role of DNA methylation in the exons and their flanking introns based on DNA methylation and expression data.

Results

Our data consists of 32000 exons with RNA-seq expression and BS-seq methylation data from Human Fibroblast cell-line IMR90 [1]. Further we extract four intronic regions of length 200 bp flanking each exon representing the middle of upstream intron, the immediate region upstream intron region, immediate intron region downstream and the middle of the downstream intron.

Strikingly we noticed a significant difference in the methylation pattern of intronic regions flanking highly methylated exons versus low methylated exons. Specifically, the highly methylated exons (figure 1A) were found to be significantly more methylated than their intronic surroundings while the low methylated exons (figure 1B) showed the opposite pattern, where the flanking introns had higher methylation levels.

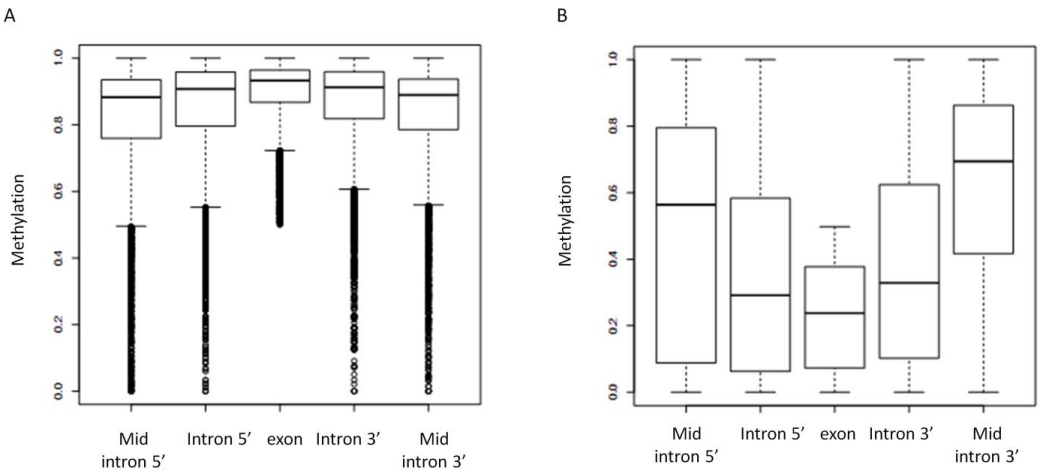

Figure 1: Methylation levels in exons and flanking introns for high [A] and low [B] methylated exons.

Furthermore, the highly methylated exons were highly expressed while low methylated exons were on general weakly expressed. Interestingly, in both top and lowest expressed exons we notice two distinct patterns of methylation (we name Peak and Dip), suggesting two alternative mechanisms relating intragenic DNA methylation to exon expression. Overall, the different methylated patterns were not correlated with either the GC content or the evolutionary conservation of the exons and their flanking introns.

Last, we explore the relation between promoter methylation and exon methylation and expression. While we did not detect a linear correlation between exon/intron methylation levels and the promoter methylation, we show that highly methylated exons tend to have higher promoter methylation and accordingly lower expression.

Conclusions

Consistent with recent studies [2], this study reinforces that the differential methylation level of the exon and its intronic surroundings can dictate exon faith. Specifically we show a positive correlation between intragenic methylation and exon expression. Overall our results strongly suggest that exon expression is influenced by the local methylation state, independent of the overall expression of the gene and the methylation status of its promoter.

References

[1] Lister R. et al, *Human DNA methylomes at base resolution show widespread epigenomic differences*, Nature 462, 315-322.

[2] Gelfman S. et al, *DNA-methylation effect on cotranscriptional splicing is dependent on GC architecture of the exon-intron structure,* Genome research, March 15, 2013