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Multitissue DNA methylome profiling during onset of salmon maturation

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Protocol Information

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Group: Salmon Multiomics

Summary: Background:Atlantic salmon farming promotes growth in conditions which mean animals may complete sexual development at weights below harvest size leading to a reduction in productivity. This prompted us to investigate the biological mechanisms that control the timing of sexual maturation. We performed a time course experiment, whereby animals were manipulated with photoperiod before tissues were collected across the time window when animals commence sexual development. We performed whole genome bisulfite sequencing (WGBS9 of three salmon tissues (pituitary, ovary and liver) at both the beginning and end of the experiment (T1 and T4), to take a first look at the patterns of DNA methylation and examine how they change in response to the onset of an important life history trait. Results:Comparison across timepoints revealed 6,373 differentially methylated regions (DMRs), of which approximately 50% were located within genes (DMGs). The ovary underwent the most profound remodelling, with a strong bias towards increased methylation levels (hyper-methylation) specially at gene bodies (gene body methylation). The majority of differentially methylated genes (DMGs) in ovary were hypermethylated (n=1165; 74%) and significantly enriched for three biological process (GO-BP), one cellular component (GO-CC) and 24 molecular function (GO-MF) terms including those with maturation-related functions such assemaphorin/glutamate receptor activity. We also performed deep transcriptomic profiling (RNA-seq) of the same tissues to explore the relationship between methylation changes and gene expression. Weak correlation was observed considering all available genes, suggesting methylation may not be the key epigenomic regulator of global expression in the context of our experiment. However, the identification of significant transcriptional and methylation changes allowed

us to explore the dynamic between these two processes by assessing the overlap of genes declared as both DEG and DMG. The overlap was low and non-significant for liver (38 / 616 or 6% of DMGs were also DEGs) and pituitary (11 / 762 or 1.4% of DMGs were DEGs). Strikingly, 195 or 14% of ovary DMGs (195 / 1357) were also differentially expressed, a number that exceeded random expectation in 83.8% of 1000 permutations tests. This suggests changes in methylation status may directly control gene expression in this subset of genes. If true, we would expect to see correspondence between the directionality of the expression and methylation changes. This appeared to be the case, as 82% of upregulated genes (148 / 179; Binomial P-value = 8.727E-20) were hyper-methylated at T4 relative to T1, matching the classical expectation of gene body methylation mediated control of gene expression (Neri et al 2017, Arechederra et al 2018). The 148 genes were enriched for 3 GO-CC terms related to chromatin remodelling complexes (SWI/SNF and nBAF) and the associated genes displayed coordinated expression and methylation status.Conclusion and implications:Taken together, the results confirmed that while methylation alone does not control genome-wide patterns of gene expression, it plays a key role upregulating a defined set of genes during the maturation process. Co-analysis of transcriptome and DNA methylome in ovary suggests chromatin remodelling genes play a role in the commitment of animals to the sexual maturation pathway. These results also open the way for the identification of functional variants that can be used in advanced breeding approaches to boost productivity in Atlantic salmon farming.References:Neri, F. et al. Intragenic DNA methylation prevents spurious transcription initiation.Nature 543, 72–77 (2017).Arechederra, M. et al. Hypermethylation of gene body CpG islands predicts high dosage of functional oncogenes in liver cancer. Nat. Commun. 9, 3164 (2018).

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