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**Adaptive phenotypic plasticity and epigenetics paper response**

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For this response, I’m going to focus on the two papers that concentrated on methylation, Ryu et al. (2018) and Liew et al. (2018). Both groups sought to link epigenomic patterns (specifically differential methylation) to observed phenotypic plasticity or acclimation. Both claimed that this relationship is poorly understood and few examples are to be found in the literature on their respective fish and coral systems.

Ryu et al. examined whether DNA methylation could explain previously observed differences in metabolic plasticity among coral reef fish exposed to warmer ocean temperatures over one or two generations. They were looking for a causal relationship between transgenerational plasticity and methylation. To this end, Acanthochromis polyacanthus individuals were exposed to +3C temperature conditions after F1 parents were raised in +0C (developmental), +1.5C (step-wise) and +3C (transgenerational) conditions, and a control group experienced no change in temperature in both generations. They collected and analyzed genomic, transcriptomic, and methylomic datasets, and important findings include the following: A) Differentially expressed regions (DMRs) were most distinct in the transgenerational group compared to the other three treatments; B) Differential methylation of nearly 200 genes was significantly correlated with metabolic phenotype (e.g. NAS), providing evidence for epigenetic regulation of core metabolic genes in response to temperature change; and C) Out of the thousands of DMGs identified in this study, only 36 were also differentially expressed, and when annotated these were found to be functionally diverse.

There are a couple of components of this paper that I believe are not particularly useful or effective at conveying what the authors found. First, the figures aren't very helpful in my opinion. In Figure 1, the experimental setup visualization is excellent, but the reporting of "ome" sizes (1a - lower half) and DMR distribution (1b) would be much easier to digest in graphical form rather than as glorified tables. Figure 1C is helpful, but even here I had trouble determining whether DMRs could belong to both a CpG Island *and* a promoter region or an exon. Pie graphs like this make it seem like groups are mutually exclusive, but unless I'm understanding CpG islands and shores incorrectly, these regions can span different sections of the genome. By comparison, Figure 1A in Liew et al. (2018) more clearly splits categories into two tiers. In fact, Liew et al. much more effectively report genome-wide patterns in methylation activity. Lastly, the DMR heatmaps didn't really provide much visually (e.g. Fig. 2a,b), possibly because the contrast between groups doesn't look that strong (although they are arguing that differences exist here). Maybe in class we can talk about ways to visualize differential expression and methylation aside from heat maps, somehow reducing or summarizing the information visually for the main paper and leaving these individual DEG/DMR plots to the supplementary material. To that end, we might also discuss why in particular we’d like to see Figure 4 as it is currently presented, instead of some sort of chart showing differences in methylation across repeats, exons, and introns for selected genes. Perhaps GO category differential expression is a way to do this, as the categorization helps de-clutter things a bit.

In Liew et al., as above, the authors would like to know if their target organism's plastic response to projected environmental scenarios is at all related to epigenetic processes. Unlike Ryu et al., Liew et al. are not specifically focused on transgenerational plasticity. They instead test for patterns in methylation across 4 different pH treatments that range from 7.2-8.0. They find that: A) most methylation occurs in genic regions, not intergenic regions; B) Most of this methylation occurs in introns, not exons; C) These patterns are consistent with the idea that methylation contributes to the reduction in “spurious transcription”, which occurs when RNA polymerase improperly initiates transcription within a gene not at the beginning; and D) Many genes involved in cell growth pathways were differentially methylated and expressed.

One important aspect of Liew's approach that was less apparent in Ryu et al. was the former’s testing for reproducibility across different methods, which they did at least twice, each time with pairing broad and targeted methods. First, when they identified via GLMs that certain genes were differentially methylated across pH treatments, the authors confirmed the differential expression via amplicon-specific bisulfite sequencing. Differential methylation results were strongly correlated for this subset of genes between WGBS and ASBS methods. Second, when RNA-seq uncovered DEGs associated with cell growth GOs, their differential expression was verified via RT-qPCR. Confirmation of changes in both methylation and expression in important gene pathways associated with plastic phenotypes instilled much greater confidence in their findings.

*References:*

Liew, Y. J., Zoccola, D., Li, Y., Tambutté, E., Venn, A. A., Michell, C. T., … Aranda, M. (2018). Epigenome-associated phenotypic acclimatization to ocean acidification in a reef-building coral. *SCIENCE ADVANCES*, 11.

Ryu, T., Veilleux, H. D., Donelson, J. M., Munday, P. L., & Ravasi, T. (2018). The epigenetic landscape of transgenerational acclimation to ocean warming. *Nature Climate Change*, *8*(6), 504–509. <https://doi.org/10.1038/s41558-018-0159-0>