RNG
Replication of Non Genome

IMEG Seminar Series

The road to global science

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Epigenetics: from stem cells to ancient DNA

This seminar series is for all students and researchers in Kumamoto University. The seminar is jointly hosted by Grant-in-Aid for Scientific Research on Innovative Areas, "**Replication of non Genome**". Check your email and find the Zoom ID and passcode !!

Our lab is studying epigenetic regulation in embryonic stem cells (ESCs) and differentiation (e.g. Schlesinger and Meshorer, Dev Cell, 2019), as well as in pluripotent stem cell-derived models of neurodegenerative diseases (e.g. Sorek et al., Genome Biol, 2021). In addition, we recently developed means to reconstruct the basic epigenetic layer, namely DNA methylation, of ancient genomes, opening up the field of "Paleo-epigenetics" (Gokhman et al., Science, 2014; Cell, 2019). My talk will be divided into two parts. I will first present work related to a recent screen for non-nuclear regulators of pluripotency we performed on an endogenously-labelled fluorescent fusion-protein library in mouse ESCs, which we previously generated (Harikumar et al., Stem Cell Reports, 2017). One of the more compelling hits was the cell cycle-associated protein, CAPRIN1. CAPRIN1, a Stress Granule (SG) component, exhibited a strikingly cyclical localization pattern in sync with mitosis, and localized to SGs, in response to stress. CAPRIN1 knockout had little effect in ESCs, but dramatically skewed differentiation and gene expression programs. RIP-seq and SLAM-seq revealed that CAPRIN1 associates with, and promotes the degradation of, thousands of RNA transcripts. CAPRIN1 interactome identified XRN2 as the likely ribonuclease. Upon early differentiation or stress, XRN2 colocalizes with CAPRIN1 inside SGs in a CAPRIN1-dependent manner. We propose that CAPRIN1 regulates an RNA degradation pathway operating during early ESC differentiation, eliminating undesired spuriously transcribed transcripts in ESCs.

In the second, shorter part, will discuss our recent work on using DNA methylation in archaic genomes to identify differentially methylated genes between modern and archaic humans. We find that genes associated with face and vocal tract anatomy went through particularly extensive methylation changes. Specifically, we identify widespread hypermethylation in a network of face- and voice-affecting genes, including NFIX, suggesting higher expression levels in archaic humans (Gokhman et al., Nat Commun, 2020). To test whether the effects of NFIX on voice box anatomy extend also to vocalization, we generated NFIX-over-expressing transgenic (Tg) mice. Vocalization recordings demonstrated significant changes in vocalizations in both male and female NFIX Tg mice compared with WT littermates. Taken together, our results demonstrate that comparative epigenetics is a powerful tool in revealing the genetic basis of human-specific traits.

References

Gokhman, D. et al., Science *344*, 523–527 (2014); Gokhman, D. et al., Cell *179*, 180-192.e10 (2019); Gokhman, D. et al., Nat Commun *11*, 1189, (2020); Harikumar, A. et al., Stem Cell Reports *9*, 1304–1314, (2017); Schlesinger, S. and Meshorer, E., Dev. Cell *48*, 135–150, (2019); Sorek, M. et al., Genome Biol *22*, 73, (2021).

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