From one stem cell to many fates: A single-cell epigenetic roadmap of planarian differentiation.

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Pluripotent stem cells can differentiate into all adult cell types, yet the mechanisms enabling this diversity remain a central question in biomedical and regenerative biology. A key component is gene regulation. DNA is packaged into chromatin, whose accessibility determines gene activity: open chromatin permits expression, whereas closed chromatin restricts it. Stem cells generally exhibit a more open chromatin state, while differentiated cells display largely closed regions. It is therefore thought that pluripotent stem cells generate diverse cell types by selectively opening and closing specific genomic regions.

Recent genome-wide methods have advanced our understanding of chromatin accessibility and interactions, and their disruption is linked to cancer and disease. However, how stem cells coordinate these dynamics to execute full differentiation programs remains unclear.

To address this, we will measure chromatin accessibility and interactions at single-cell resolution in the planarian *Schmidtea mediterranea*, an ideal *in vivo* model. Unlike most animals, adult planarians retain pluripotent stem cells that continuously generate all cell types, enabling whole-body regeneration from small fragments.

We will functionally perturb candidate epigenetic regulators using RNA interference, targeting multiple chromatin regulatory complexes. The effects will be analysed using a highly multiplexed single-cell approach integrating transcriptomic, chromatin accessibility, and chromatin conformation data within the same cells across differentiation.

By linking gene perturbation to chromatin changes, we will define how conserved regulators control genome accessibility in specific cell types. This work will provide a comprehensive view of chromatin remodelling during stem cell differentiation, informing strategies in human stem cell biology and regenerative medicine.