Interplay between Polycomb and 3D chromatin architecture during cell fate commitment

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How do cells know which genes to keep on—and which to shut off—when committing to a new fate? Polycomb group proteins are best known for silencing developmental regulators through H3K27me3, but their role goes far beyond histone marks. By organizing the genome into three-dimensional repressive hubs, Polycomb complexes help sculpt chromatin architecture and ensure that alternative lineages remain silent. In this talk, I will explore the dynamic interplay between Polycomb-mediated repression and 3D genome topology during cell fate transitions, using iPSC-to-cardiomyocyte differentiation as a model. I will highlight how disruption of this coordination destabilizes cellular identity, unleashing inappropriate gene programs and impairing lineage maturation. These insights reveal how epigenetic regulation and spatial genome organization converge to enforce robust cell fate commitment, with broad implications for reprogramming, disease, and regenerative medicine.