Epigenetics : Polycomb and gene regulation in development and cancer

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The complex process of cellular differentiation depends on precise control of gene expression specific to each cell lineage. The Polycomb Repressive Complex 2 (PRC2), which includes EZH1 and EZH2 as catalytic subunits along with core components EED and SUZ12, plays a key role in this regulation. PRC2 controls gene silencing by adding methyl groups to H3K27 and compacting chromatin. Differences in expression levels, methyltransferase activity, and chromatin compaction ability between PRC2-EZH1 and PRC2-EZH2 suggest they have unique roles in development and disease. While the function of PRC2-EZH2 is relatively well-studied in development and cancer, the distinct functions of PRC2-EZH1 remain unclear.

Our study on cardiomyocyte differentiation shows that EZH1 predominantly influences late-stage cardiomyocyte maturation, exhibiting non-redundant functions with EZH2. Advanced sequencing techniques uncover EZH1 mediates 3D chromatin interaction, leading to the formation of *de novo* H3K27me3-repressive chromatin domains in cardiomyocytes, which repress neuro-lineage and cell cycle regulating genes. Depletion of EZH1 results in the de-repression of neuronal lineage genes and indicating defects in cardiomyocyte function. This research enhances our understanding of PRC2 function beyond early development, shedding light on the intricate interplay between EZH1 and EZH2 in regulating gene expression during cellular differentiation, particularly in the context of heart function.

In the cancer context, we characterized an EZH1-specific mutation EZH1 Q571R, which is commonly found in thyroid cancer. We found that PRC2-EZH1^{Q571R} showed significant increase in histone methyltransferase (HMT) activity than PRC2-EZH1^{WT} via its enhanced nucleosome binding and DNA compaction *in vitro*. Using an isogenic thyroid epithelial follicular cell line expressing either EZH1^{WT} or EZH1^{Q571R}, we confirmed that EZH1^{Q571R} leads to greater deposition of H3K27me3, more effective formation of closed chromatin and inhibits the expression of tumor suppressor genes. Our studies unveil the underlying molecular patho-mechanism of PRC2-EZH1^{Q571R} in follicular thyroid cancer.