PRC2: a Novel Regulator of Ovarian Folliculogenesis

Ellen G. Jarred[1]; Gabrielle Pulsoni[1]; Reena Desai[2]; Dagmar Wilhelm[3]; David Handelsman[2]; Patrick S. Western[1]

1. Centre for Reproductive Health, Hudson Institute of Medical Research, Clayton, Victoria, Australia and Department of Molecular and Translational Science, Monash University, Clayton, Victoria, Australia.
2. ANZAC Research Institute, Concord, New South Wales, Australia.
3. Department of Anatomy and Physiology, The University of Melbourne, Parkville, Victoria, Australia.

The development of unique cell types in multicellular organisms is achieved through careful coordination of gene expression, involving signalling, transcription factors and epigenetic modifications. Tight regulation of the epigenome is therefore critical for normal cell function and epigenetic modifications are often disrupted in disease, including cancer. This has led to development of drugs to specifically target epigenetic modifiers for cancer treatment. Despite substantial influence of epigenetic modifications on cell identity and function, very little is understood about the epigenetic regulation of ovarian development or how dysregulation of epigenetic modifications contributes to ovarian dysfunction in women. Polycomb Repressive Complex 2 (PRC2) is a widely conserved epigenetic modifier which catalyses the repressive modification Histone 3 Lysine 27 trimethylation (H3K27me3). While PRC2 regulates cell function and identity in many developmental contexts, whether PRC2 regulates somatic cell development and function in the ovary is unknown. Using a combination of genetic and pharmacological mouse models and human granulosa tumour cells (KGN cells), we investigated how reduced PRC2 function impacts ovarian function. We demonstrate that PRC2 is essential for normal granulosa cell proliferation, follicular development and steroidogenesis in mouse ovaries. Further, the PRC2 inhibitor MAK683 substantially reduced both H3K27me3 and proliferation of KGN cells, suggesting PRC2 may also regulate proliferation in human granulosa cells and could be a useful target for treatment of specific ovarian cancers. These findings provide functional evidence that PRC2 is an essential regulator of follicle development and female endocrine regulation. Our work generates important insights into epigenetic regulation of ovarian development, with potential implications for understanding disorders of female reproductive health for which abnormal granulosa cell function and steroid production have roles, such as granulosa cell tumours, primary ovarian insufficiency and infertility, and how emerging PRC2 inhibiting drugs may impact both healthy ovarian tissue and ovarian cancer cells.