Integrative analysis of reference epigenomes for uterine endometrium

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Abstract

Endometrium, the inner layer of uterus, is essential for successful conception. It undergoes a cycle of regeneration, proliferation, differentiation and desquamation several hundred times during the reproductive age under the control of the ovarian steroidal hormones, estrogen and progesterone. Although these dynamic morphological and functional changes during the menstrual cycle are considered to be epigenetically regulated, information on epigenetic regulation in the endometrium has so far been very limited. Endometrium is mainly composed of fibroblastic stromal and glandular epithelial cells. Decidualization of endometrial stromal cells and various factors secreted by the glandular epithelium are crucial for embryo implantation, development and maintenance of pregnancy. The remarkable regenerative capacity of endometrium is considered to be supported by the presence of endometrial stem/progenitor cells. Therefore, endometrium has been regarded to be a potential source of mesenchymal stem cells for regenerative medicine.

In this study, we aimed to build the reference epigenomes of the endometrial stromal cells (EMSCs) and epithelial cells (EMECs) isolated from the endometria of their proliferative and secretory phases for the first time. By conventional cell isolation protocols, whereas it was easy to obtain a large number ($> 10^7$ cells) of EMSCs by cell culture due to their high proliferative potential, the number of EMECs obtainable was limited ($< 10^5$ cells). We overcame this obstacle by establishing a modified protocol, which enabled us to isolate more than 1 x 10^6 of both EMECs and EMSCs with over 95% purity reproducibly from a single total hysterectomy case without a long term cell culture (*J Rprod Dev* 62:213, 2016).

We have obtained ChIP-seq data for a core set of six histone modification marks (H3K4me3, H3K27ac, H3K4me1, H3K36me3, H3K9me3, and H3K27me3) for EMECs and EMSCs isolated from proliferative and secretory phases of the endometria from three individuals. We subjected our ChIP-seq dataset to the ChromHMM software, and annotated the chromatin states of genomic intervals by their combinatorial patterns of histone modification marks for each types of cells. We are currently cataloguing EM-specific, EMSC-specific, and EMEC-specific enhancers, and trying to extract their genomic and functional features. DNA methylome and transcriptome sequencing are also in progress for the same sample set.

Our epigenome dataset will facilitate elucidating epigenetic regulation underlying the dynamic remodeling of endometrial tissue during each menstrual cycle, and also serve as a reference to search for epigenetic abnormalities at pathogenic states such as endometriosis as well as to explore potential therapeutic targets.

Key words: Endometrium, endometrial stromal cells (EMSCs), endometrial epithelial cells (EMECs), reference epigenome, ChromHMM