Proprotein Convertase and its Associated Remodeling of Extracellular Matrix are Potential Targets for the Discovery of a Non-Hormonal Contraceptive

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The development of non-hormonal contraceptives with less side effects creates an equal opportunity for women to plan their pregnancy, with ovulation as a primary druggable target. The objective of this study is to investigate the role of proprotein convertase in ovulation. We hypothesize that proprotein convertase critically contributes to the remodeling of extracellular matrix (ECM) and the rupture of follicular wall during ovulation. Immature mouse ovarian follicles isolated from 16-day-old CD-1 female mice were cultured using our established encapsulated in vitro follicle growth (eIVFG) model. Mature follicles grown from eIVFG were treated with 1.5 IU/mL human chorionic gonadotropin (hCG) to induce ovulation in vitro. Follicles were collected at 0, 1, 4, and 8 hours for RNA-sequencing (RNAseq) analysis. Results showed that a few genes in the proprotein convertase gene family were significantly increased by the hCG stimulation, including proprotein convertase subtilisin/kexin-3 (Psck3), Pcsk5, and Pcsk 6. In situ RNA hybridization validated the temporal expression of these genes, and these genes also had consistent expression patterns between follicles from eVIFG and in vivo mouse models. We next co-treated mature follicles with hCG and proprotein convertase inhibitor (PCI) at 0, 1, 5, and 10 µM and found that PCI dose-dependent inhibited follicle rupture without affecting the secretion of progesterone. The following in situ zymography experiment further revealed that PCI at 10 µM remarkably decreased hCG-induced activation of matrix metalloproteinases (MMPs) during in vitro ovulation. Taken together, these results suggest that proprotein convertase and its associated MMP activation and ECM remodeling are essential for ovulation, presenting druggable targets for developing a non-hormonal contraceptive. Supported by R25ES020721, The Bill & Melinda Gates Foundation, INV-003385, K01ES030014, and the Rutgers Office of Research and Economic Development.