Endometrial Regeneration and Micro-engineered Platform: Possible Solutions for Subfertility

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South Korea’s fertility rate, already the world’s lowest, has dropped yet again. There are problems in overcoming subfertility due to difficulties in uterine regeneration because of uterine fibrosis and inflammation. In addition, absence of a model that can sufficiently reflect the uterine environment is a bottle neck to fully understand uterine microenvironment. In this seminar, I would like to present two possible solutions to overcome subfertility in the perspective of regenerative medicine and 3D in vitro modeling. First, tissue-specific decellularized extracellular matrix recapitulates the complexity of natural ECMs, creating an organ-specific microenvironment based on its intrinsic characteristics. Here, we developed hydrogels containing uterus-derived decellularized extracellular matrix (UdECMs) from the endometrium specific layer or the entire uterus. UdECMs served as effective organ-specific biomaterials, displaying that intrauterine UdECM administration induced endometrial regeneration and fertility enhancement. Moreover, UdECM administration altered the profile of natural killer cell subpopulations to exhibit more mature and less cytotoxic features, providing a favorable uterine environment for successful implantation and decidualization. We discovered insulin-like growth factor 1 and insulin-like growth factor-binding protein 3 as key regulatory factors that contribute to UdECM-mediated endometrial regeneration. Second, the endometrium is a highly specialized multi-layered organ in the human body that plays crucial roles in maintaining the patency of the uterine cavity. Although numerous animal studies have demonstrated the cyclic physiology of the endometrium, there remain substantial discrepancies among different species. Moreover, the lack of a physiologically relevant in-vitro model for the endometrium, with the given practical difficulties associated with access to primary cells and in-vitro maintenance of the multi-layered culture system, remains the main obstacle for research, suggesting the need for a more physiologically relevant model for the human endometrium. Here, our representative microengineered vascularized endometrium on-a-chip closely recapitulates the endometrial microenvironment that consists of three distinct layers including epithelial cells, stromal fibroblasts and endothelial cells in a 3D extracellular matrix in a spatiotemporal manner. Our endometrium chip can be used for a better understanding of the molecular and cellular mechanisms underlying menstrual cycle and implantation process.