DYSREGULATED EXPRESSION OF AGED EXTRACELLULAR VESICLES IN MOUSE UTERUS INDUCES ENDOMETRIAL FIBROSIS BY REGULATING MACROPHAGE POLARIZATION

Jungwoo Shin, Heeseon Yang**,** Nanum Chung, Sangheon Jung.

1Department of Translational Medicine, Seoul National University College of Medicine, Seoul 03080, Republic of Korea2Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam 13620, Republic of Korea, 1Department of Translational Medicine, Seoul National University College of Medicine, Seoul 03080, Republic of Korea 2Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam 13620, Republic of Korea, 1Department of Translational Medicine, Seoul National University College of Medicine, Seoul 03080, Republic of Korea 2Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam 13620, Republic of Korea, 1Department of Translational Medicine, Seoul National University College of Medicine, Seoul 03080, Republic of Korea 2Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam 13620, Republic of Korea.

Abstract Body

Endometrial (EM) fibrosis is the key factor in decreasing fertility and is related to uterine aging. Infertility treatment with assisted reproductive technology could improve the pregnancy rate in women with decreased fertility. However, still, there is no definitive treatment method for infertility caused by EM fibrosis. In this study, we investigated the mechanism of fibrosis in the aged EM. C57BL/6 mice aged 2, 6, 10, 16, and 20 months were used in this study which represented an equivalent human age range of young adult to elderly. First, we evaluated the fibrotic markers in the aged uterus. Endometrial fibrosis drastically increased with aging, especially in the metestrus phase when the macrophage is activated. Macrophage number and polarization between young and aged uterus were assessed using flow cytometry and immunohistochemistry. The number of macrophages significantly increased in the aged uterus and M1/M2 macrophage polarization was markedly different between young and aged uterus, meaning macrophages may play a role in the aged uterus. To investigate if endometrial cell-derived extracellular vesicles (EVs) induce macrophage polarization which controls fibrosis, EVs were isolated from young and aged uterine fluid, and then miRNA profiling was performed. We identified 848 miRNAs in young and aged EVs and found that 93 miRNAs are significantly different between the two groups. Interestingly, 13 miRNAs related to macrophage polarization were significantly differentially expressed between young and aged EVs. Also, cytokine composition related to the immune response is determined by cytokine array in young and aged EVs. The cytokine array results showed a significant up-regulation of macrophage polarization-related cytokines in the aged EVs. These results suggest that EVs from the aged uterus may be directly involved in regulating macrophage polarization, which causes EM fibrosis.