ImmunoTools *special* Award 2025

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Estrogen-induced inflammatory dysregulation of endometriotic stromal cells

Endometriosis is a chronic, hormone-sensitive disease in reproductive age women, which characterizes with extrauterine invasion of endometrial-like tissue in peritoneal cavity and pelvic organs. The condition presents with hampered endometrial differentiation (process of decidualization), attenuated fertility (correlates with implantation failure, recurrent abortions, low success in *in vitro* fertilization procedures), negative impact on general health and quality of life in patients. Surgical intervention and histological validation of ectopic endometriotic implants remains the gold standard for diagnosis of the disease but concomitantly the laparoscopy links to higher risk of side effects and morbidity in the subjects. Therefore, intensive scientific efforts are focused on finding non-invasive approaches for diagnostics and follow-up of the disease. Symptoms of severe and chronic pain are reported by ~75% of patients. Possible causes for this symptom include cytokines, nociceptive mediators and estrogen. The pathophysiologic causes of the disease are not known but increased levels of IL-1β, TNFα are associated with the growth and persistence of endometriosis. Many reports show the prevalence of different inflammatory and inti-inflammatory molecules in biological fluids[1]. Cytokines play a crucial role in proliferation, differentiation, adhesion, invasion, angiogenesis and immune evasion of endometriotic lesions. At systemic level the maintenance of chronic inflammation and immune dysregulation/evasion are also documented. Current notion supports the idea that the cytokines are a consequential result from enhanced and dysregulated estradiol activity. Specifically, estradiol is synthesized in the endometriotic tissue, which in turn responds with estrogen-dependent proliferation and invasion[2]. On the other hand, the lesions are progesterone resistant. They show aberrant endometrial differentiation since the action of estrogen cannot be inhibited, and the proliferation of stromal cells suppressed.[3] The lack of response to progesterone hinders the suppression of the inflammatory phenotype in the condition.

Our previous results have shown a disparate receptor repertoire of endometrial stromal cells (ESC) from healthy and endometriosis lesions in response to pro-inflammatory

cytokines IL-1β, TNFα and IFNγ in a model of chronic inflammation. Cytokines treatment activates separate signaling pathways with distinct outcome in the membrane adhesion receptors in healthy and diseased ESC. By virtue, the adhesion molecules reflect the functional state of stromal cells and are involved in diverse functions, such as migration, proliferation, signaling, intercellular communications etc. Therefore, we are interested in investigating the mechanistic and circumstantial states of endometriotic stromal cells in inflammatory and endocrine conditions.

Pro-inflammatory (IL-1β) phenotype of ESC from endometriotic implants will be investigated to elucidate the contribution of ESC to dysfunctional tissular environment. By using a cell culture model, the adhesion profile of eutopic and ectopic stromal cells will be compared to cells from healthy women under inflammatory conditions. In tissues, cytokines define the profile of leukocyte recruitment and activity of the infiltrating and resident cells. Therefore, the usage of an antagonist (IL-1RA) of inflammation-mediated signaling will be investigated as a potential rescue mechanism of the condition. Endometriotic lesions from patients will be studied by immune fluorescence for adhesion receptors distribution (integrin alphaV, integrin beta1, CD90) to evaluate the mechanistic relevance of the model. A supplementary approach with IGFBP1 treatment (a decidualization protein)[4] will be used in an attempt to rectify the functionality of endometriotic ESC. It is expected that the analysis of adhesion molecules would provide new insights for deciphering inflammatory response and other behavior changes in the endometriotic ESC.

The selected *ImmunoTools* products will be used to analyze the IL-1 β secretory phenotype of endometriotic stromal cells upon hormonal induction. A cell-based model of the disease microenvironment will be simulated by cytokines to screen the functional response and the dysregulated signaling of endometriotic stromal cells. It is expected that this study could help understand the interdependence between the inducible membrane changes in endometriotic stromal cells due to chronic inflammation.

References:

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