The understanding of molecular mechanisms of interactions between macrophages and endometrial fibroblasts in processes related to pathogenesis of endometrosis in mares

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Equine endometrosis (*chronic degenerative condition*) is defined as an active or inactive fibrotic process that develops around the endometrial glands and in the stroma, often associated with pathological alterations in the endometrial glands within fibrotic foci. Generally, fibrosis is characterized by excessive extracellular matrix (ECM) deposition and fibroblast activation. Inflammation is associated to development of fibrosis in a paracrine way by the secretion of profibrotic cytokines and other factors from injured tissues and inflammatory cells. Inflammatory mediators act on endometrial cells and then affect fibrogenesis and ECM remodeling. Macrophages (MΦ) are recruited at the sites of injury or infection and their secretion products affect the surrounding microenvironment. There are at least two different macrpohages populations: “classically” activated MΦ1 and “alternatively” activated MΦ2. Both MΦ1 and MΦ2a have been noted to be involved in the pathogenesis of fibrosis in other organs. However, their effect on mare endometrial fibroblasts remains unclear. In our project, we put forward the hypotheses that (a) the endometrial ratio of MΦ1 and MΦ2a is altered in favor of MΦ2 in the course of endometrosis; (b) MΦ1 enhance development of equine endometrosis through effect on secretion of profibrotic inflammatory mediators from endometrial fibroblasts and on myofibroblast differentiation; (c) MΦ2a promote the development of endometrosis by increasing cell proliferation, migration, and deposition of extracellular matrix components (ECM); (d) the action of factors secreted by MΦ1 and MΦ2a is mediated by WNT/β-catenin, Hippo signaling pathways and action of metallopeptidase (MMP)-9. The specific objectives of the project include testing the effects of activated MΦ1 and MΦ2a on: (1) endometrial fibroblast properties, secretory function, ECM deposition in *in vitro* and *in vivo*; (2) signaling pathway in communication between MΦ and fibroblasts.

The main objective of this project is to understand mechanisms underlying the initiation and progression of endometrosis with the aim of developing effective therapeutic strategies in treatment of endometrosis. It would be essential tool to improve horse reproductive efficiency, effective conservation and enhancement of animal genetic resources. Additionally, effective therapies to prevent or even to reverse existing fibrotic lesions are not yet available in any organ. Therefore, the understanding of the common fibrosis pathways would lead to development of these therapies in other organs and species.