Immunopathogenesis of endometriosis; an overview of the role of innate and adaptive immune cells and their mediators

Running title: Immunopathogenesis of endometriosis

Maryam Zare Moghaddam

Reproductive Immunology Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, Email: zmary1371@gmail.com,

Hossein Ansariniya

Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran,

Reproductive Immunology Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, Email: ansarssu@yahoo.com

Seyed Mohammad Seifati

Reproductive Immunology Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, Email: s.m.seifati@gmail.com

Fateme Zare

Reproductive Immunology Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, Email: fatemezare91@gmail.com Orcid ID: 0000-0002-2472-018X

Farzaneh Fesahat

Reproductive Immunology Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, Email: farzaneh.fesahat@gmail.com , Orcid ID: 0000-0002-3743-4449

***Corresponding Authors:** Dr. Fateme Zare

Reproductive Immunology Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, **Tel:** +98 353 6285406, **Postcode:** 8916188635

***Abbreviations**: ANA, Antinuclear antibodies ; APCs, Antigen-presenting cells ; BLyS, B Lymphocyte Stimulator; Btk, Bruton's tyrosine kinase ; CCL-2, Chemokine ligand 2 ; COX-2, Cyclooxygenase-2 ; CXCL10, C-X-C motif chemokine ligand 10 ; DCs, Dendritic cells; ENA-78 , Epithelial neutrophil-activating peptide ; ESCs, Endometrial stromal cells; FasL, Fas ligand; FOXP3, Forkhead box protein P3 ; IFN-γ, Interferon γ ; IL, Interleukin; MAIT, Mucosa-associated invariant T ; MCP-1, Monocyte chemotactic protein-1 ; MDSCs, Myeloid-derived suppressor cells ; NETs , Neutrophil extracellular traps ; NF- Kb, Nuclear factor-kappa B; NK cells, Natural Killer cells; PCNA, Proliferating cell nuclear antigen; PF, Peritoneal fluid; PG-E2, Prostaglandin E2; RANTES, Regulated upon Activation Normal T Cell Expressed and Presumably Secreted; TF, Transcription factors ; TH1, T helper 1 ; TH17, T helper 17; TH2, T*

helper 2; TNF-α, Tumor necrosis factor-α; Tregs, Regulatory T cells; VEGF, Vascular endothelial factor

Abstract

Endometriosis is a chronic inflammatory disease associated with the growth and proliferation of endometrial-like tissues outside the uterus. Although the exact etiology and mechanism of the pathogenesis of the disease have not been fully elucidated, the immune system cells and the mediators produced by them can be named as effective factors in the onset and progression of the disease. Abundant production of inflammatory mediators by neutrophils and macrophages and reduced cytotoxicity of defined cells promote endometriosis at the early stages of the disease. Following an increase in the inflammation of the environment, the body takes compensatory mechanisms to reduce inflammation and establish homeostasis. For this purpose, the body produces remodeling and anti-inflammatory factors leading to slow conversion of the inflammatory environment into a non-inflammatory environment with proliferative and immunosuppressive properties. Environmental conditions induce M2 macrophages, TH2 cells, and Tregs differentiation, promoting disease progression by producing angiogenic and immunosuppressive factors. However, the exact molecular mechanism involved in changing inflammatory to non-inflammatory conditions is not yet fully understood. In this study, we attempted to review studies on the role of the immune system in endometriosis to better understand the pathogenesis of endometriosis.

Keywords: Endometriosis. Adaptive immunity. Innate immunity. Immune cell. Mediator

1. Introduction