Radboudumc
university medical center

New Frontiers in Innate Immune Memory

Title: Immunomodulatory effects of trained immunity in endometriosis in mice and human

Authors: Mohamed Jeljeli [1,2], Luiza da Gama Coelho Riccio[1,4], Sandrine Chouzenoux[1], Ludivine Doridot[1], Mauricio Simões Abrão[3], Charles Chapron[1,3*], Frédéric Batteux[1,2*]

Affiliations:

[1] *Département 3I « Infection, Immunité inflammation ", Institut Cochin, INSERM U1016, Université Paris Descartes, Sorbonne Paris Cité, Paris, France.*

[2] *Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, Assistance Publique–Hôpitaux de Paris (AP–HP), Hôpital Universitaire Paris Centre (HUPC), Centre Hospitalier Universitaire (CHU) Cochin, Service d'immunologie biologique (Professeur Batteux), Paris, France.*

[3] *Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Universitaire Paris Centre (HUPC), Centre Hospitalier Universitaire (CHU) Cochin, Département de Gynécologie Obsétrique II et Médecine de la Reproduction (Professeur Chapron), Paris, France.*

[4] *Faculty of Medicine, University of São Paulo, Endometriosis Division, Obstetrics and Gynecology Department. São Paulo, Brazil.*

Topic: Innate immunity, Inflammation, endometriosis, macrophages, trained immunity

Radboudumc
university medical center

344 words

Background:
Endometriosis is a frequent chronic inflammatory and hormone-dependant gynaecological disease, characterized by the persistence and growth of vascularized endometrial tissue at ectopic sites, causing pelvic pain and infertility. If its pathogenesis remains poorly understood, immune cells and especially macrophages are thought to play a central role in lesion establishment and maintenance through driving chronic inflammation and tissue remodelling.

Aim:
Here, we aim to analyze the immunomodulatory effects of trained macrophages on the endometriotic cells implantation and to apply these properties as novel therapeutic tools.

Methods:
Two types of immune stimuli (BCG and repeated low doses of LPS "LPS^{low}") were used to train Balb/c mice in order to: i) characterize the changes in the phenotype by flow cytometry, lactate and cytokine production, epigenetic modifications of peritoneal macrophages ii) study the immunomodulatory effects of peritoneal macrophage training on endometriotic growth in a syngeneic model of endometriosis iii) evaluate the adoptive transfer of LPS^{low}-macrophages on endometriosis outcome in mice.
We then used an *in vitro* co-culture model of trained macrophages and endometriotic cells to highlight the cellular cross-talk.

Results:
BCG-training accelerated the endometriotic lesion growth along with an enhanced expression of chemokine and inflammatory receptors on peritoneal macrophages, inflammatory cytokines production and expression of type I collagen and cyclooxygenase 2 in lesions, while LPS^{low} had an opposite effect. Adoptive transfer of LPS^{low} macrophages were effective to slow down the growth and establishment of endometriotic lesions in mice and was accompanied by a decreased production of IL-6 an TNF-α but an elevated IL-10 as well as a modification of inflammatory and chemokine receptor expression.
Co-culture of in vitro LPS^{low}-trained human macrophages with endometriotic cells derived from patients with endometriosis is accompanied by a diminished inflammatory cytokines release and a decrease of the expression of gene encoding adhesion molecules and fibrosis.

Discussion:
Our findings reveal that targeting inflammation through the manipulation of trained immunity prior to endometriosis induction has a significant impact on endometriotic implantation and growth bringing a new insight in the pathogenesis of endometriosis and paving the way to promising novel therapeutic approach for this pathology.

Position presenting author: underlined
Word count of abstract body: maximal 350 words