Endometriosis as a disease of immune dysfunction

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endometriosis

noun [C]
an inflammatory disease in which endometrial-like tissue grows outside the uterus.
Endometriosis Lesion

Koga, K, editor. 2021. Immunology of Endometriosis
Lesions may originate from retrograde menstruation, transformation from stem cells, and/or tissue laid down before birth.

In some cases, superficial lesions may be physiological and not the cause of pain.
Estrogen strongly stimulates endometriosis lesions and is made by endometriosis lesions.
Progesterone should normally slow the growth of lesions and modulate immune function.
Cross-talk between nerves, (including the vagus nerve) and the immune system.
Iron activates NF-κB in macrophages.
Hypoxia signals and regulates macrophages.
Low androgen exposure in utero, probably due to environmental toxins.

Dinsdale, N et al. The evolutionary biology of endometriosis.
Epigenetic changes are transgenerational. e.g. Dioxin exposure alters hormone and immune genes for generations.
Many identified polymorphisms including:

- Polymorphisms in HLA and other genes.
- Strong correlation with SLE, RA, CD, autoimmune thyroid disease, and IBD.
Correlation with nickel allergy suggests a common underlying mechanism.

The microbiome of the vagina, peritoneal cavity, and gut affect hormones, immune function, and endometriosis.
The topic of today.

immune dysfunction
Macrophages in endometriosis: they came, they saw, they conquered

Auto-immunity and endometriosis: evidence, mechanism and therapeutic potential

Role of Th1, Th2, Th17, and regulatory T cells in endometriosis
LPS regulates the pro-inflammatory response in the pelvis and growth of endometriosis via the LPS/TLR4 cascade.
The work of science has nothing whatsoever to do with consensus. Consensus is the business of politics. Science, on the contrary, requires only one investigator who happens to be right, which means that he or she has results that are verifiable by reference to the real world.

Michael Crichton
Is the "bacterial-immune" observation the **key insight** that endometriosis research has been waiting for?
Macrophage polarisation

The process by which macrophages produce distinct functional phenotypes as a reaction to specific microenvironmental stimuli and signals.
With autoimmune disease:

- reduced natural killer cell activity
- increased number and cytotoxicity of macrophages
- abnormalities in the functions and concentrations of B- and T- lymphocytes, including T-reg cells
- polyclonal increase in the activity of B lymphocytes and the production of autoantibodies.
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The danger model

The hypothesis that the immune system does not distinguish between self and non-self, but rather between things that might cause damage and things that will not.

Valles et al. 2014
Toll-like receptors

Toll-like receptors (TLRs) are membrane-bound pattern recognition receptors (PRRs) that recognise damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs).
Crosstalk between Innate Immunity and Adaptive Immunity

- **TLRs (Toll-like receptors)**
  - Pathogen recognition
  - Phagocytosis
  - Antigen presentation
  - Co-stimulatory molecules

- **Macrophages or dendritic cells**
  - Inflammatory cytokines

- **Naïve T cells**
  - Th1: IL-2/IL-12/IFN-γ (pro-inflammatory)
  - Th2: IL-4/IL-5/IL-10/IL-13 (anti-inflammatory)
  - Th17: IL-6/IL-17 (pro-inflammatory)
  - Treg: IL-10/TGF-β (anti-inflammatory)

**Innate immunity** → **Adaptive immunity**

Koga, K, editor. 2021. Immunology of Endometriosis
underlying immune genotype + epigenetic changes

arrival of estradiol with puberty

estrogen

macrophage activation via TLR4 and NF-kB pathway

endometrial-like tissue

lesions

LPS endotoxin possibly from intestinal permeability

LPS endotoxin

dysbiosis of the vaginal microbiome

from the gut via intestinal permeability

“gut microbiota-derived extracellular vesicles”

underlying immune genotype + epigenetic changes

arrival of estradiol with puberty

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LPS endotoxin possibly from intestinal permeability

immune dysfunction incl. changes to adaptive immunity, autoantibodies, neurogenesis and angiogenesis

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Autoimmune genotype

- Strict avoidance of gluten.
- Strict avoidance of A1 casein and maybe eggs.

Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases

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LPS toxin


- Antimicrobial herbal medicine and supplements for LPS and SIBO: oregano, lactoferrin, resistant starch, Lactobacillus GG, and berberine. Lui et al. 2017 Berberine inhibits the LPS-induced proliferation of the inflammatory response of stromal cells of adenomyosis tissues mediated by the LPS/TLR4 signaling pathway.

PMCID: PMC5740511
PMID: [29285168](https://www.ncbi.nlm.nih.gov/pubmed/29285168)

Berberine inhibits the LPS-induced proliferation and inflammatory response of stromal cells of adenomyosis tissues mediated by the LPS/TLR4 signaling pathway

Li Liu, Li Chen, Caixia Jiang, Jing Guo, Yan Xie, Le Kang, and Zhongping Cheng
Immune-supporting nutrients

- zinc
  - Messali et al. 2014. The possible role of zinc in the etiopathogenesis of endometriosis.
- retinol
- selenium
- N-acetyl cysteine
- vitamin D
- curcumin
- resveratrol
  - Dull et al. 2019. Therapeutic approaches of resveratrol on endometriosis.
- medicinal cannabis

- iodine (1-3 mg) but only if thyroid antibodies are NOT detectable
Lipiodol (ethiodized oil) inhibits peritoneal lymphocyte and macrophage activity and upregulates NK, dendritic, and Treg cells.
Other considerations

- other gut pathogens
- mast cell activation
- mold-related illness or CIRS
- oral micronised progesterone
- pelvic floor therapy
- amygdala retraining
- address history of trauma
- vagus nerve
- downregulate NF-kB
- low nickel diet
- melatonin.
Endometriosis lesions are not always the explanation for pelvic pain.
Immune dysfunction plays a major role in the pathogenesis of endometriosis.
Look to the gut and LPS endotoxin
Consider gluten and other immune disruptors
Nourish and support a healthy immune and nervous system
Questions?

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References