

Endometriosis as a disease of immune dysfunction

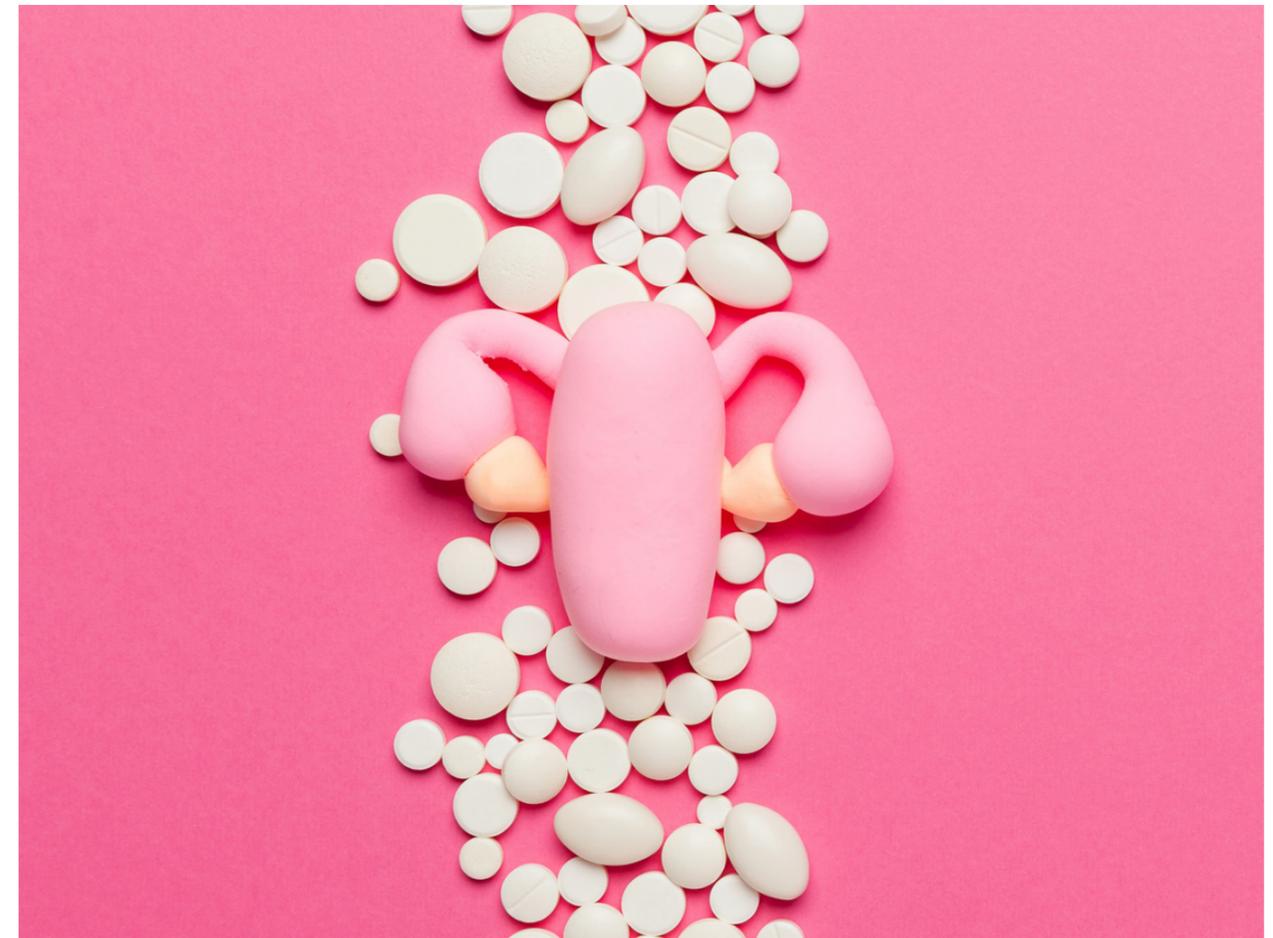
Dr Lara Briden, ND
October 2022



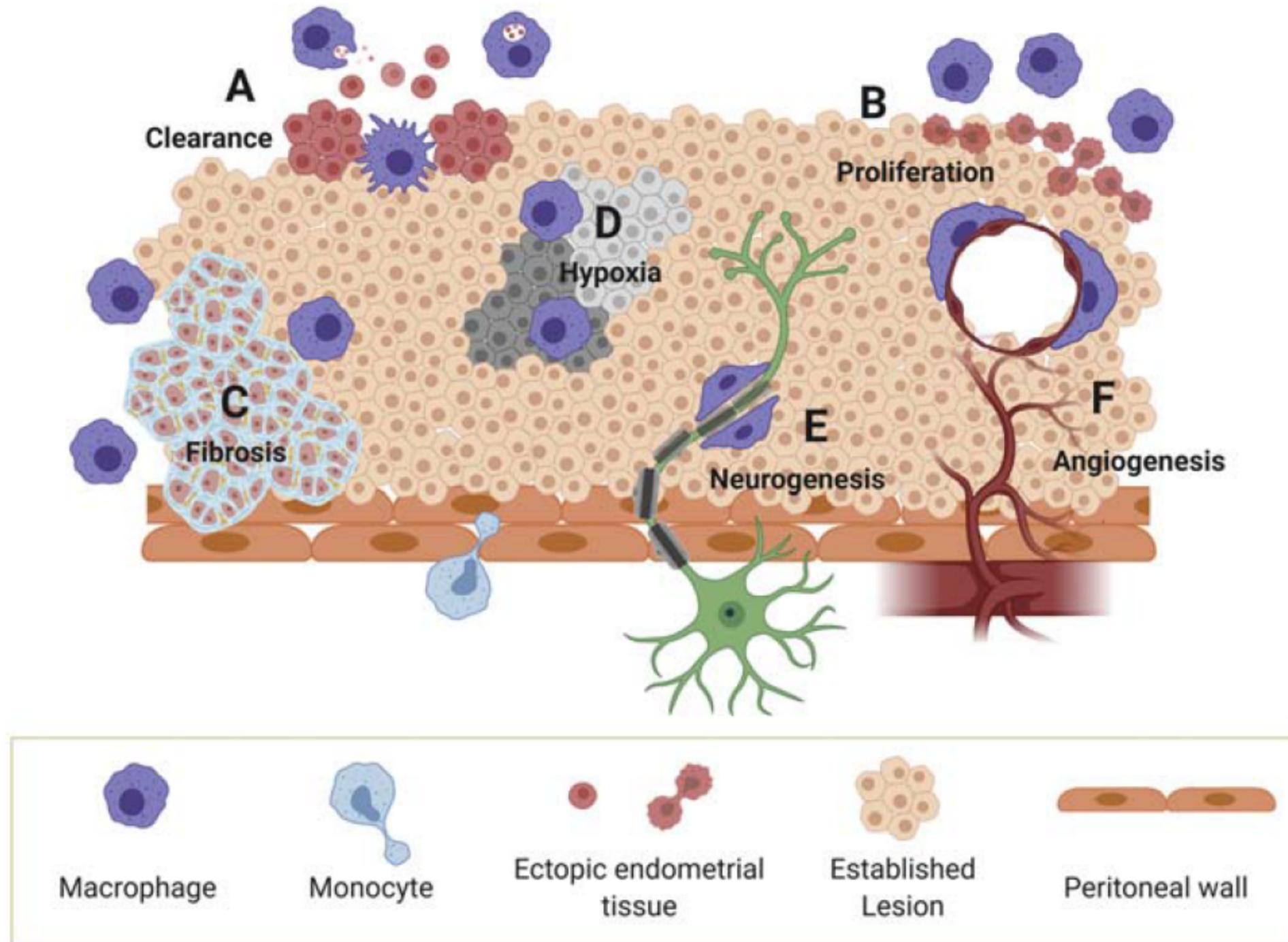
endometriosis

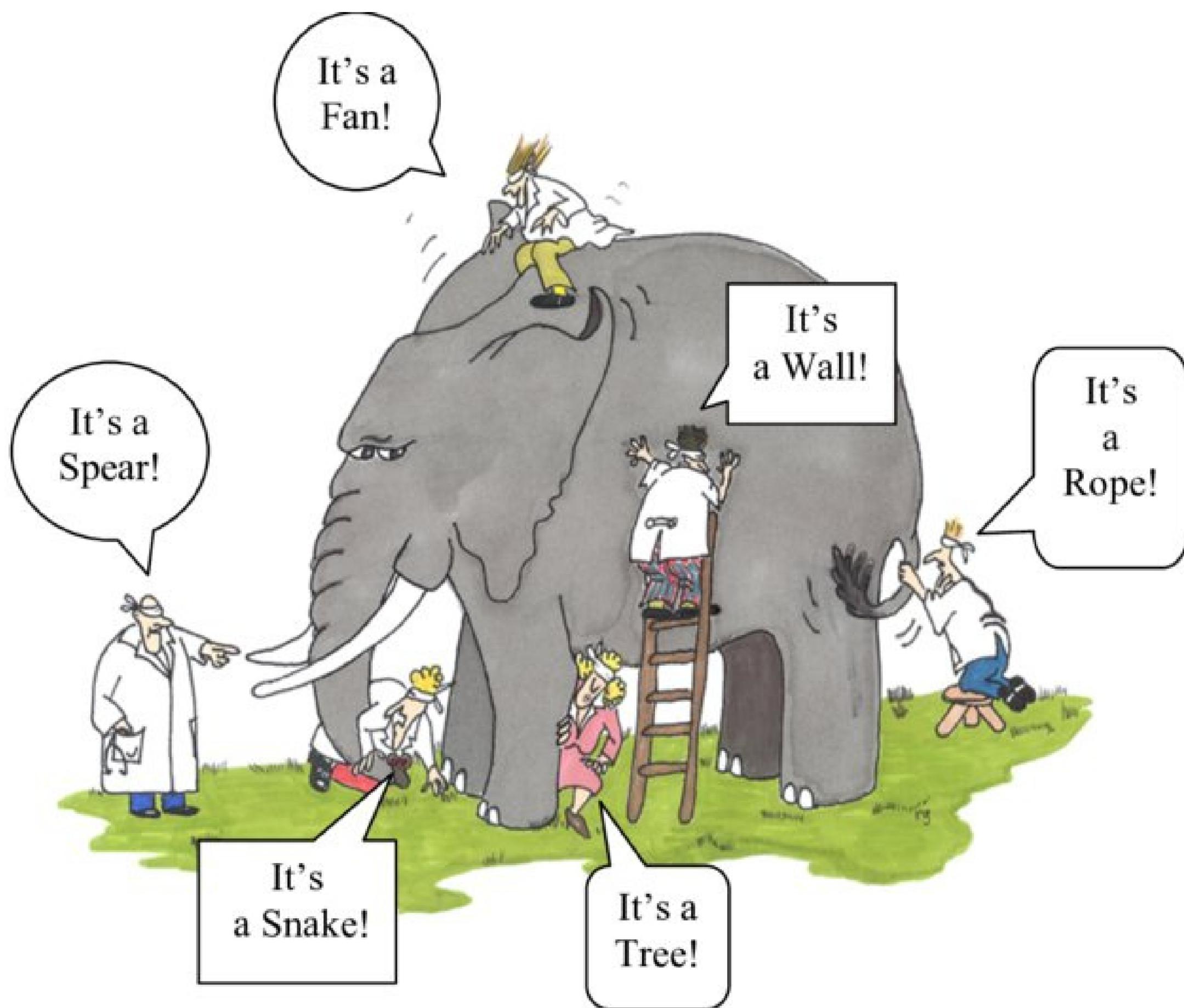
noun [C]

an inflammatory disease in which endometrial-like tissue grows outside the uterus.



Endometriosis Lesion





It's a Fan!

It's a Wall!

It's a Rope!

It's a Snake!

It's a Tree!

It's a Snake!



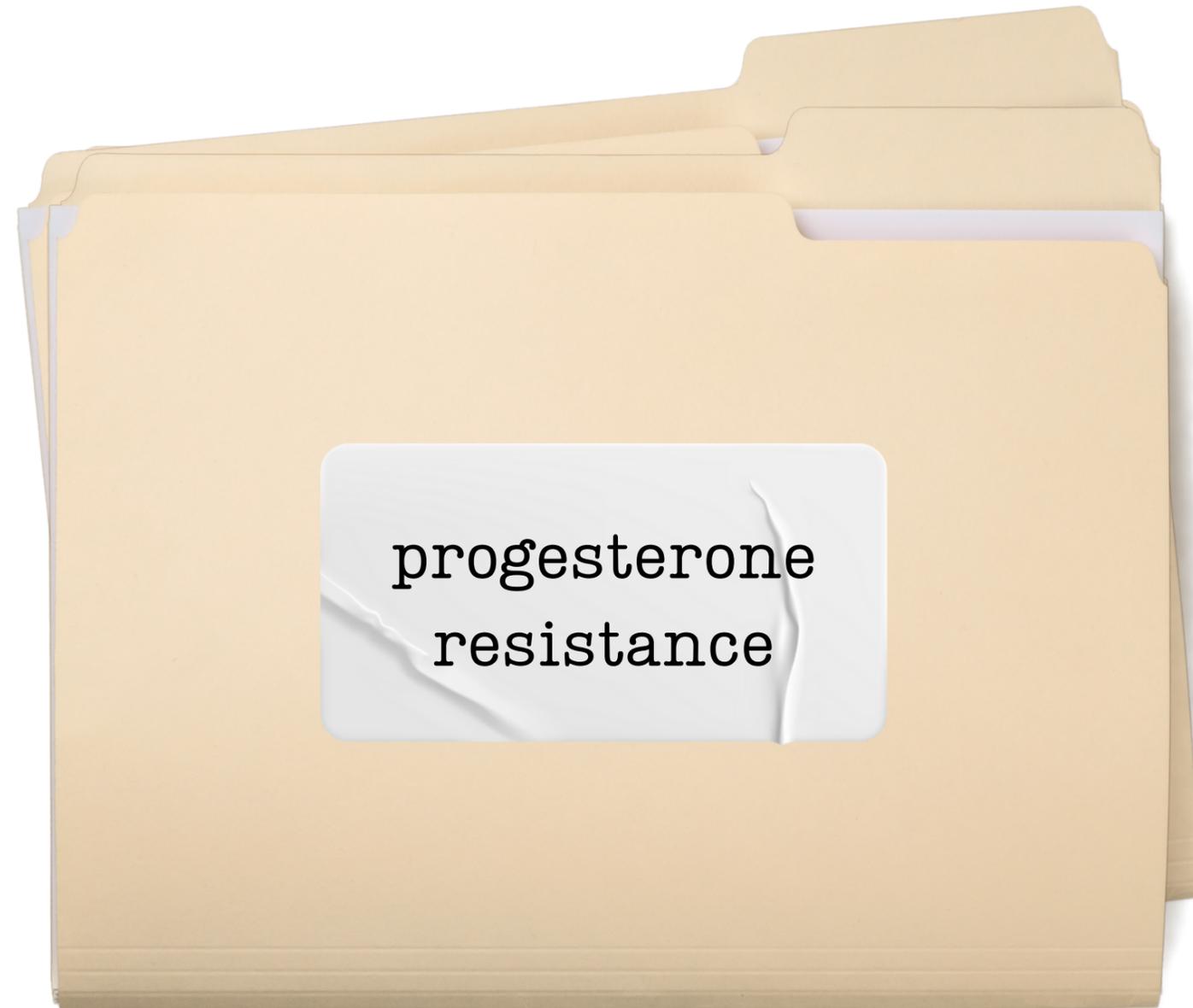
presence of
the lesions

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- κ B in
macrophages.



Hypoxia signals and
regulates macrophages.



low androgen
exposure in utero

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.

Borghini, R et al. Irritable Bowel Syndrome-Like Disorders in Endometriosis: Prevalence of Nickel Sensitivity and Effects of a Low-Nickel Diet. An Open-Label Pilot Study.



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



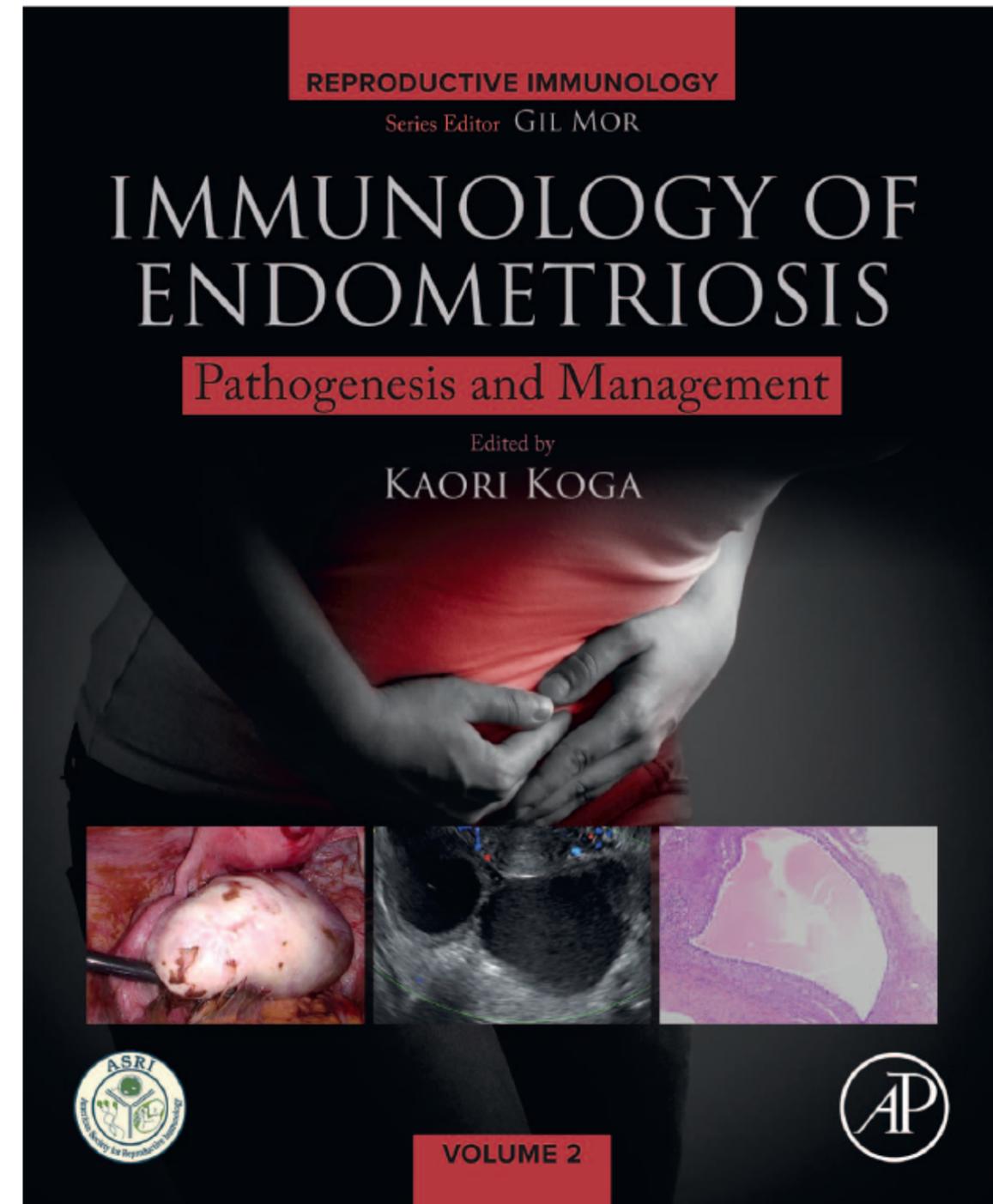
The topic of today.



Koga, K, editor. 2021.

***Immunology of
Endometriosis:
Pathogenesis and
Management –***

Reproductive Immunology.
Elsevier Inc.



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

Bacterial contamination hypothesis: a new concept in endometriosis

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Abstract

Background: Endometriosis is a chronic disease that mainly affects women of reproductive age. The exact pathogenesis of this disease is still debatable. The role of bacterial endotoxin (lipopolysaccharide, LPS) and Toll-like receptor 4 (TLR4) in endometriosis were investigated and the potential role of endotoxin in the pelvic environment was examined.

Methods: The limulus amoebocyte lysate test was used to measure the endotoxin levels in the menstrual fluid and peritoneal fluid and their potential role in the growth of endometriosis was investigated. Menstrual blood and endometrial samples were cultured for the presence of microbes. The effect of gonadotrophin-releasing hormone agonist (GnRHa) treatment on intrauterine microbial colonization (IUMC) and

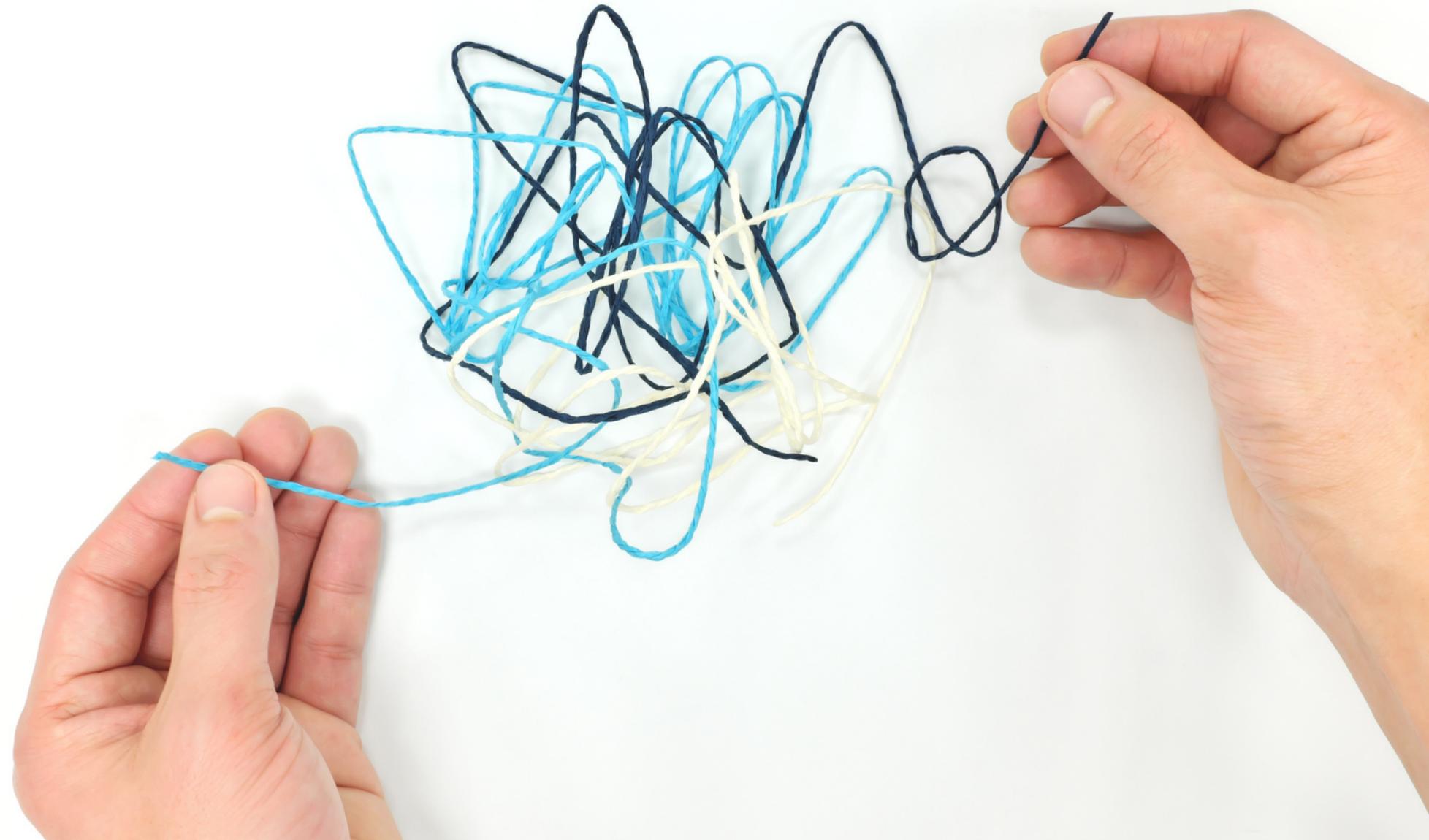
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LPS regulates the pro-inflammatory response in the pelvis and growth of endometriosis via the LPS/TLR4 cascade.
— ” —

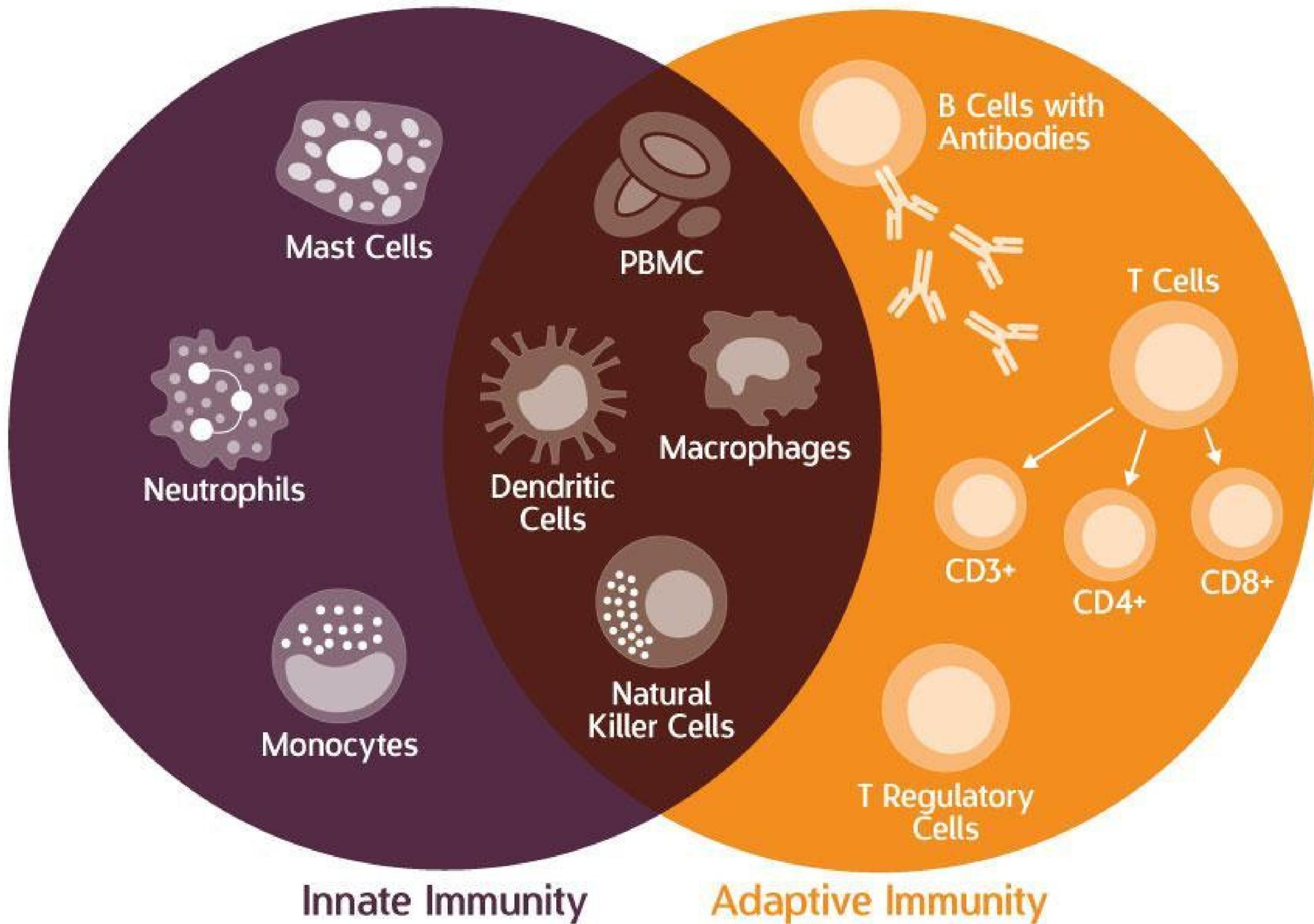
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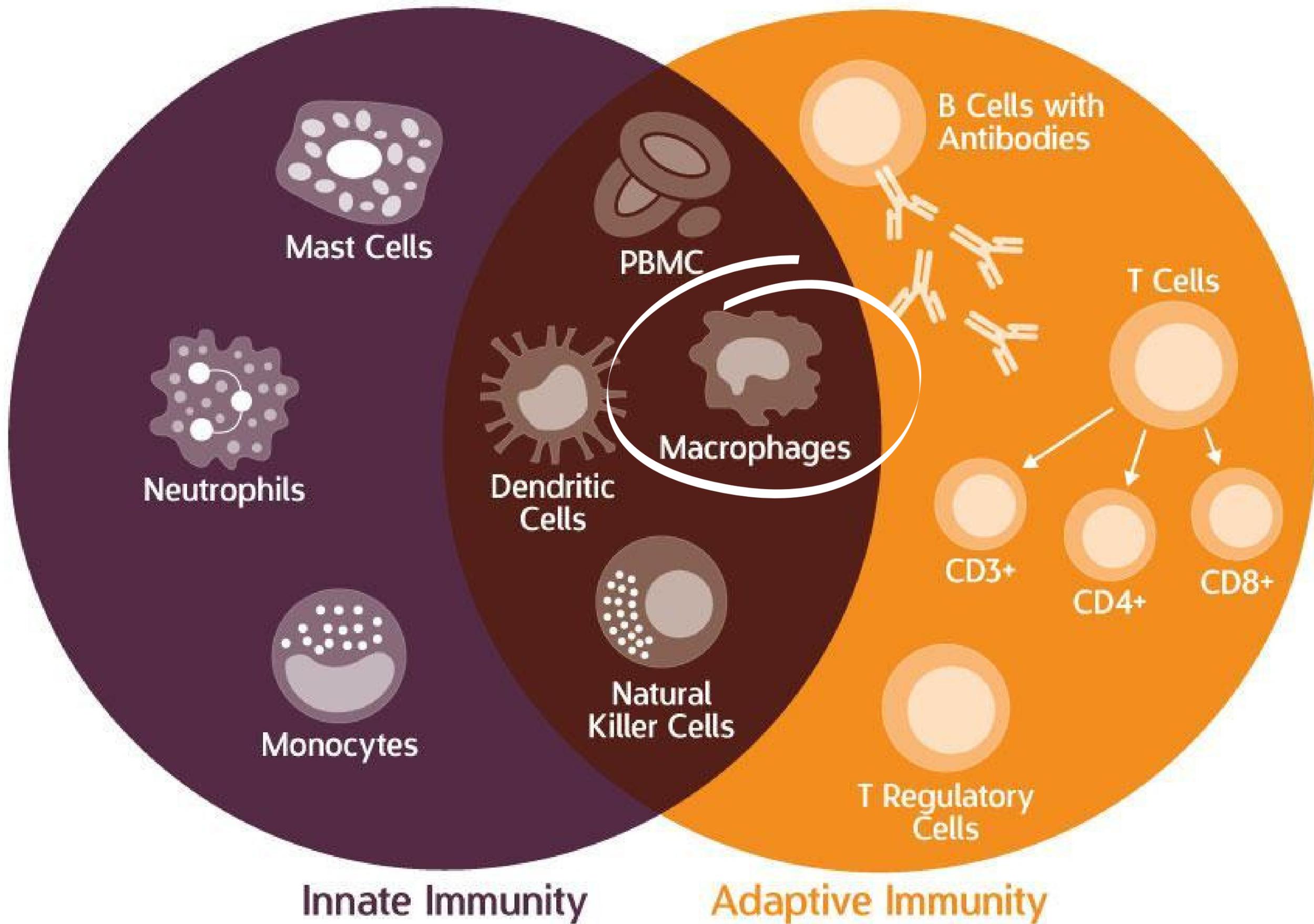
The work of science has nothing whatsoever to do with consensus. Consensus is the business of politics. Science, on the contrary, requires only one investigator who happens to be right, which means that he or she has results that are verifiable by reference to the real world.

Michael Crichton

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



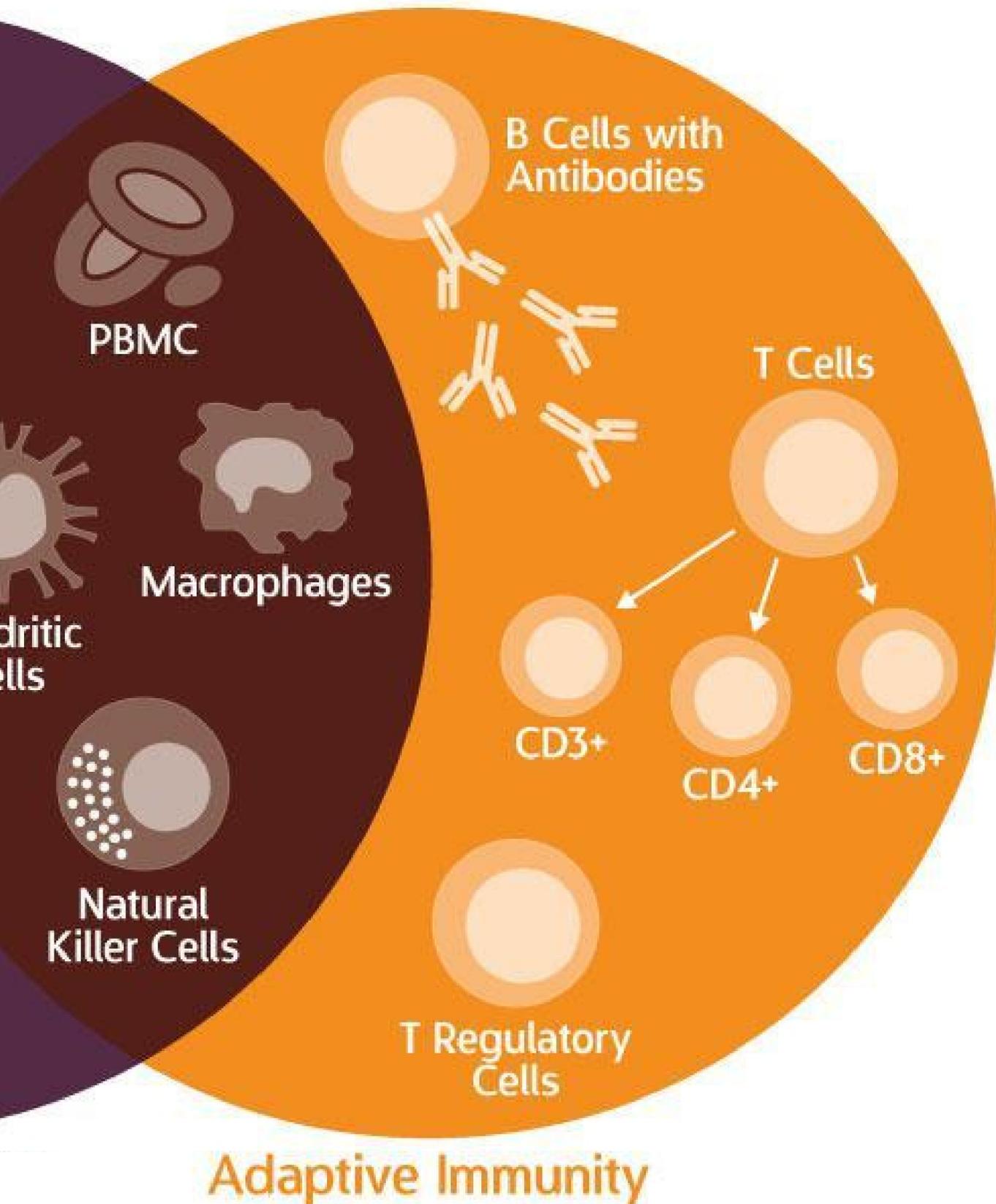




Macrophage polarisation

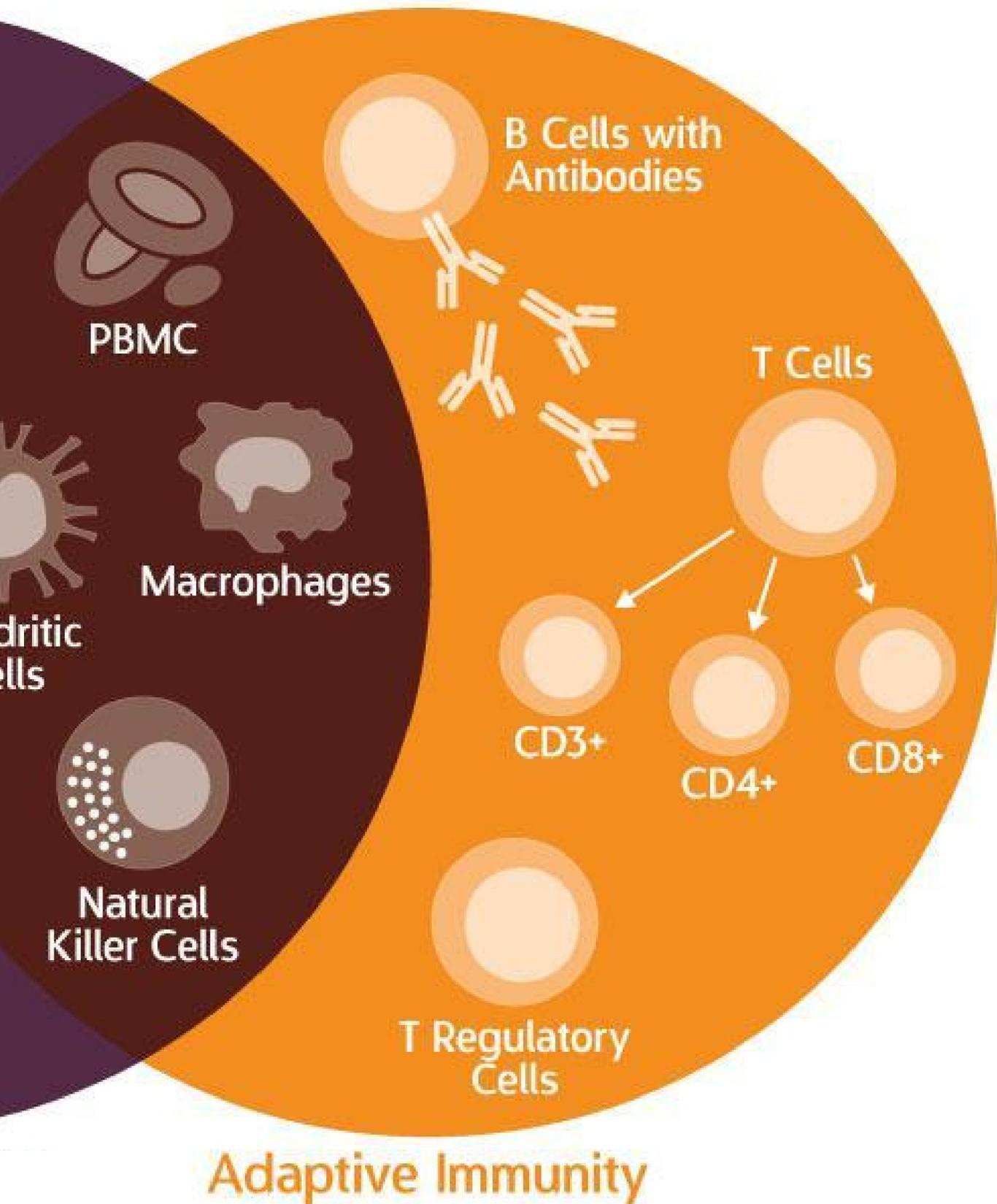
The process by which macrophages produce distinct functional phenotypes as a reaction to specific microenvironmental stimuli and signals.





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**.

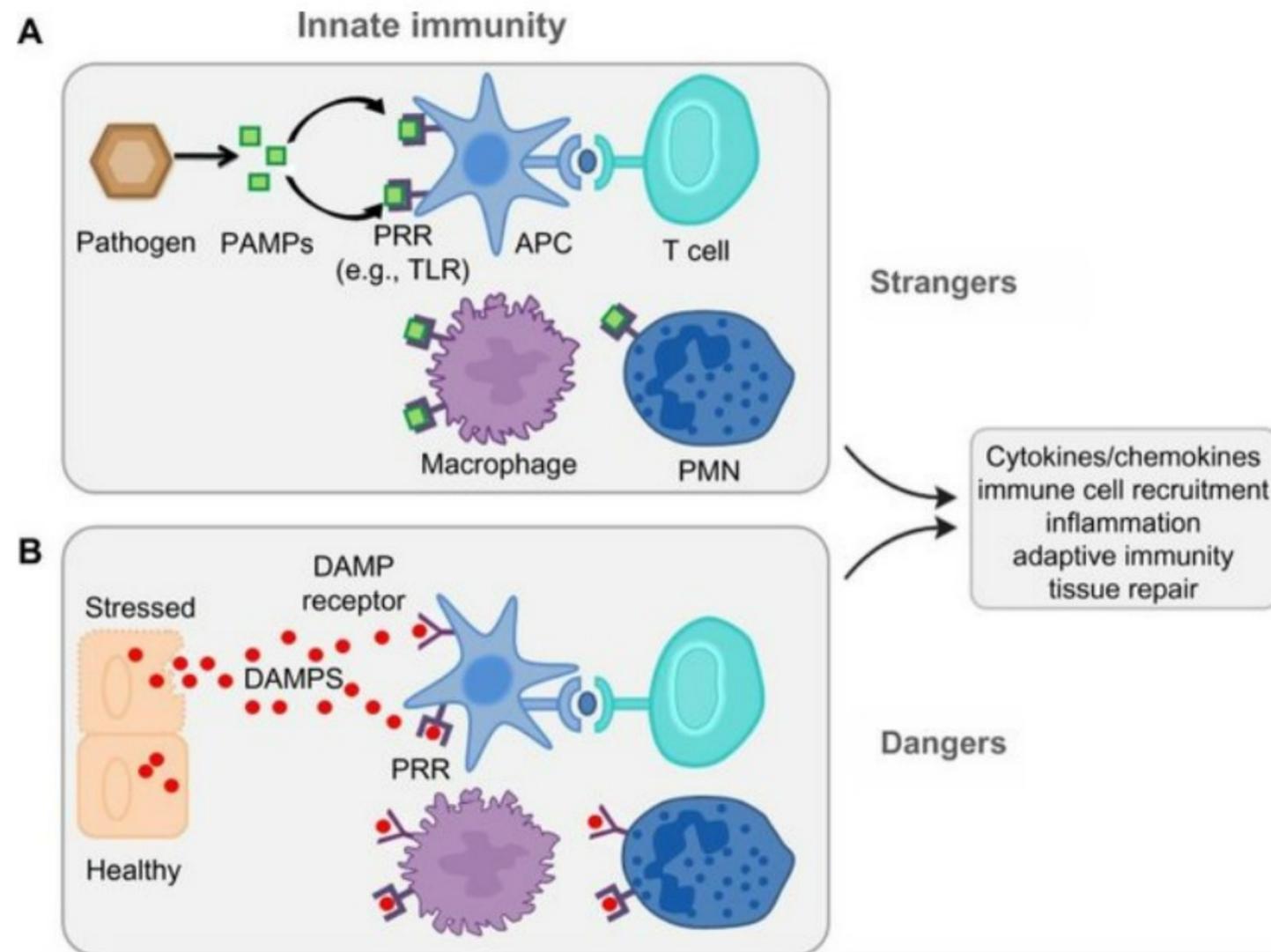


With autoimmune disease:

- reduced natural killer cell activity
- increased number and cytotoxicity of macrophages
- abnormalities in functions and concentration of lymphocytes,
- polyclonal increase of B lymphocytes of **autoantibodies**

anti-endometrial and antiovary antibodies

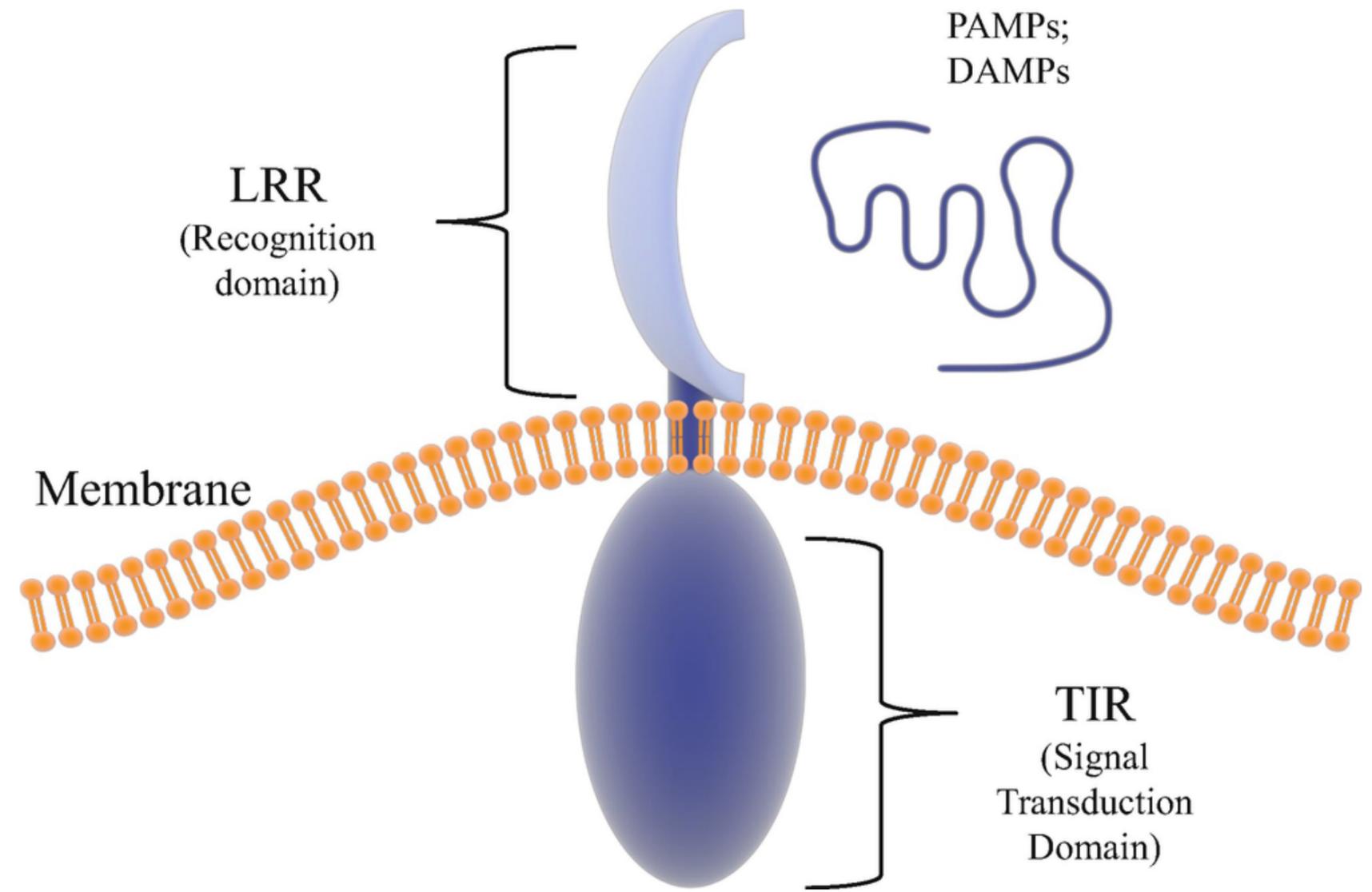
The danger model



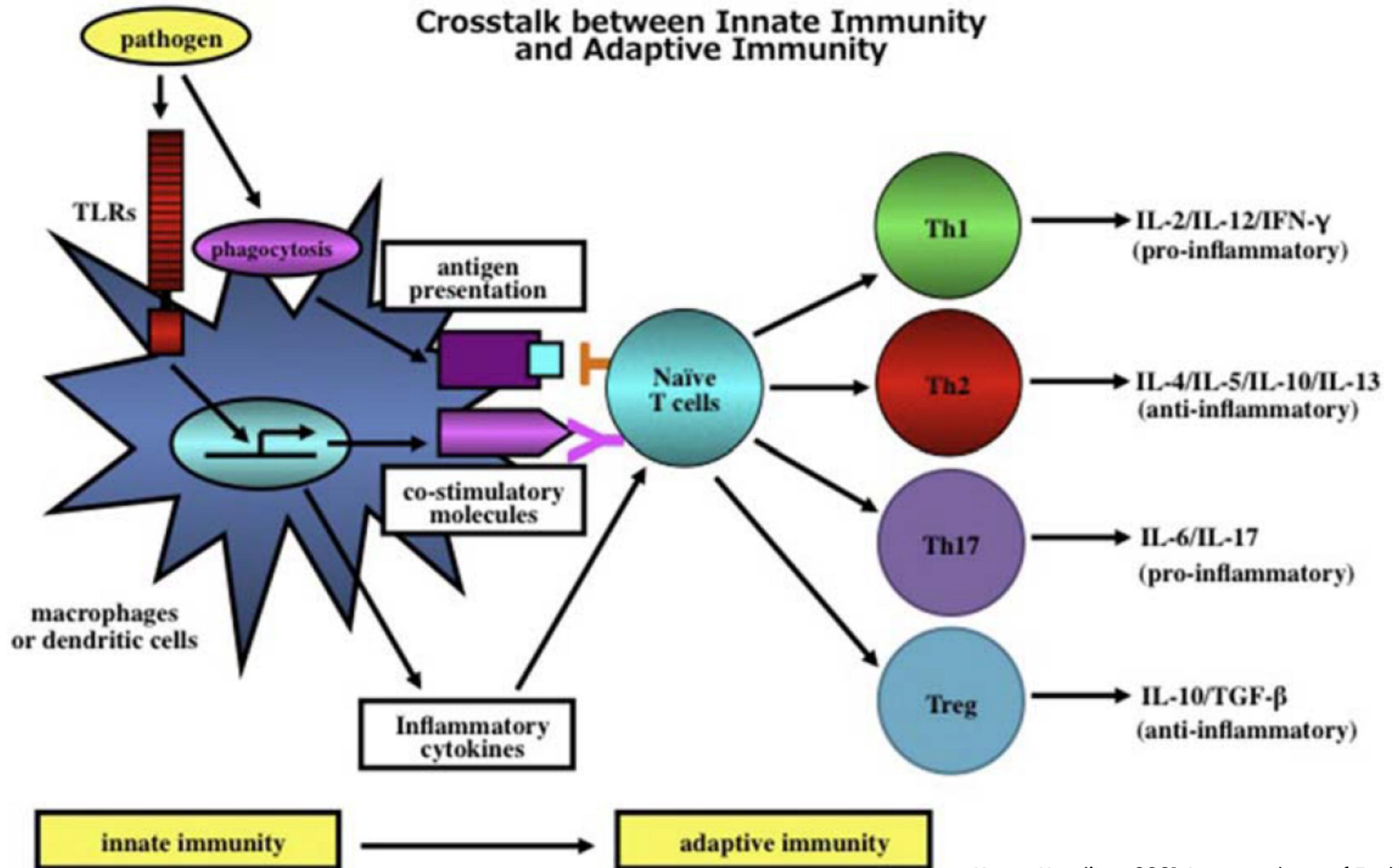
The hypothesis that the immune system does not distinguish between self and non-self, but rather between things that might cause damage and things that will not.

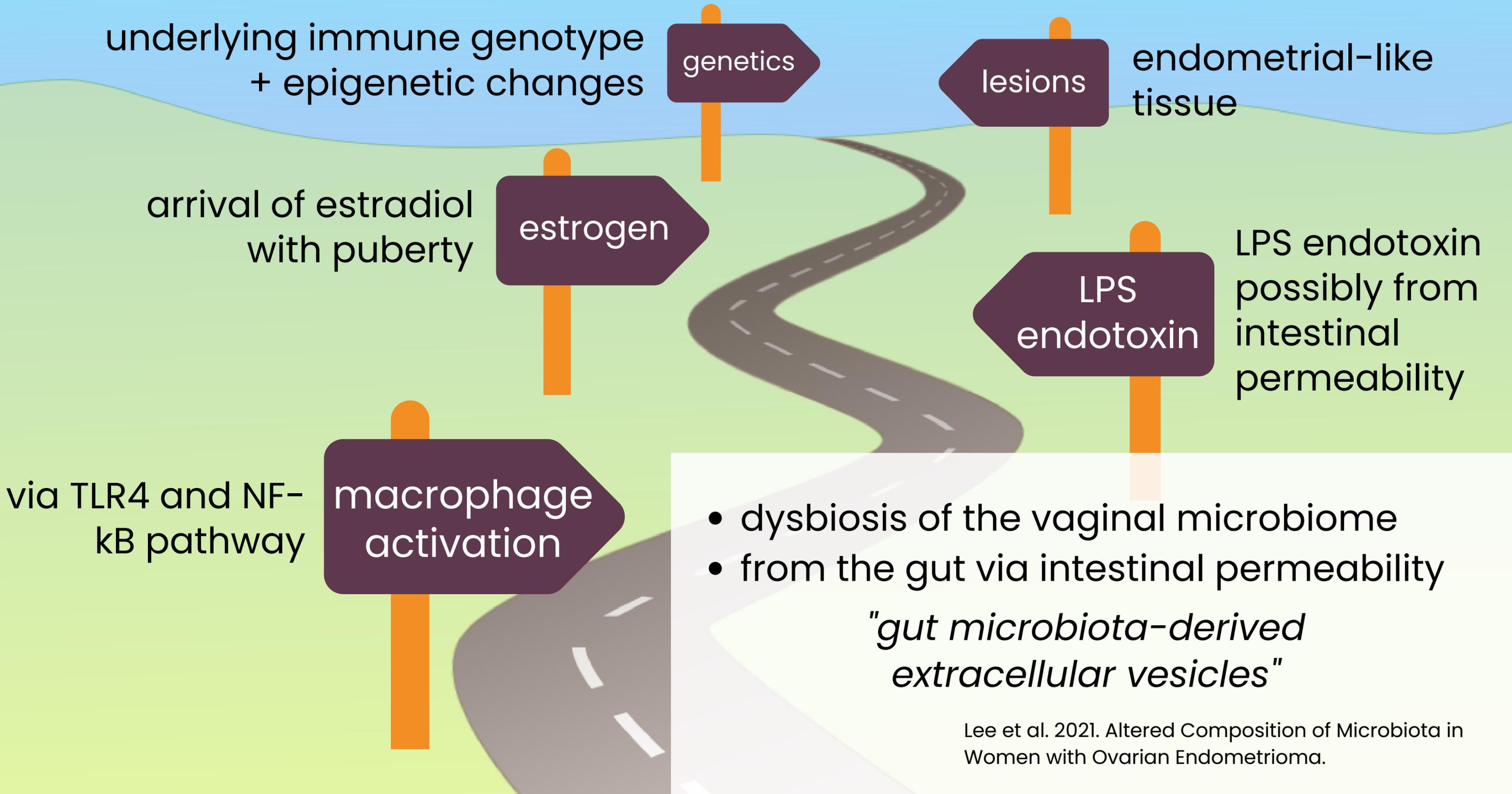
Toll-like receptors

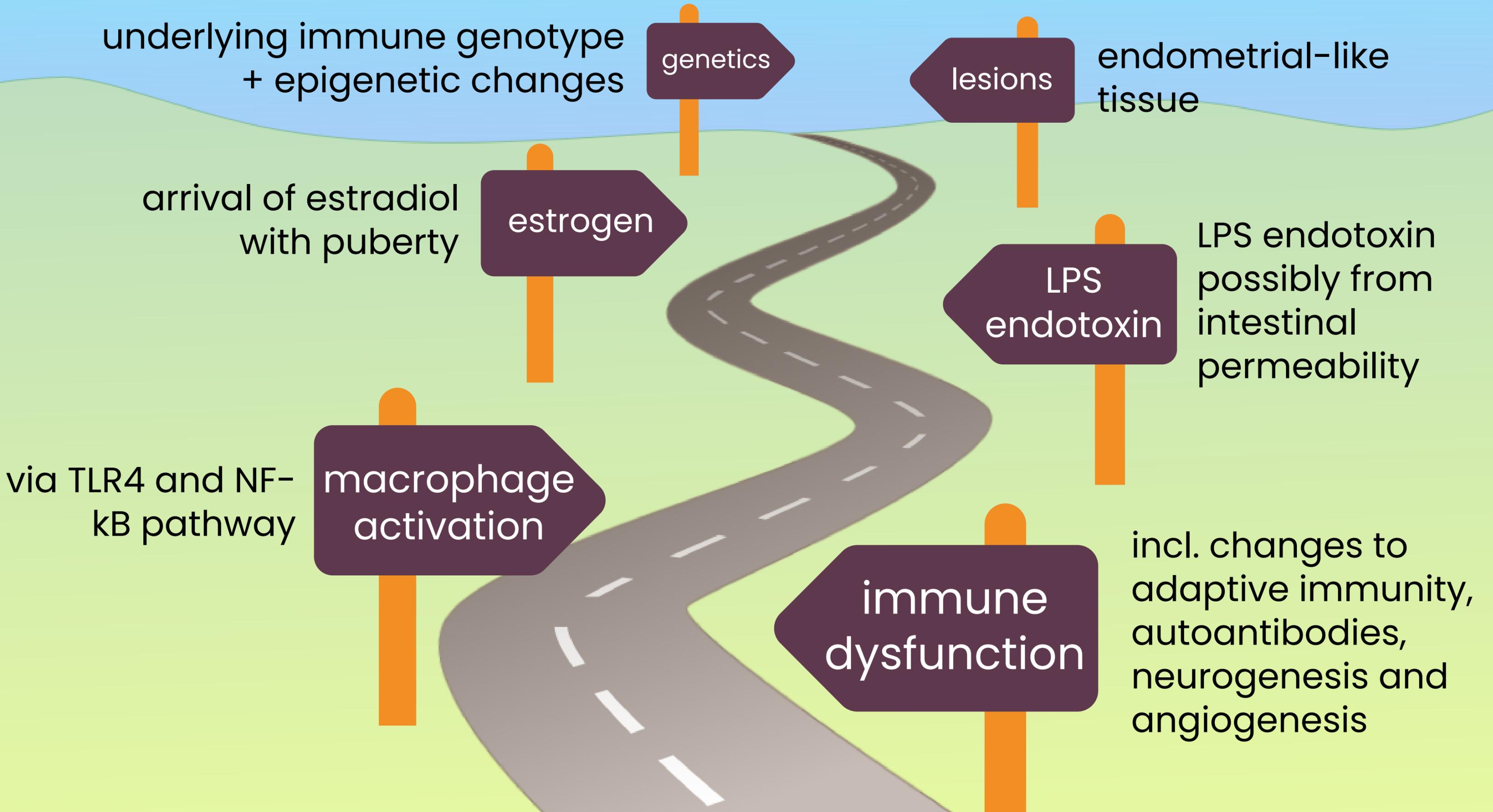
Toll-like receptors (TLRs) are membrane-bound pattern recognition receptors (PRRs) that recognise damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs).

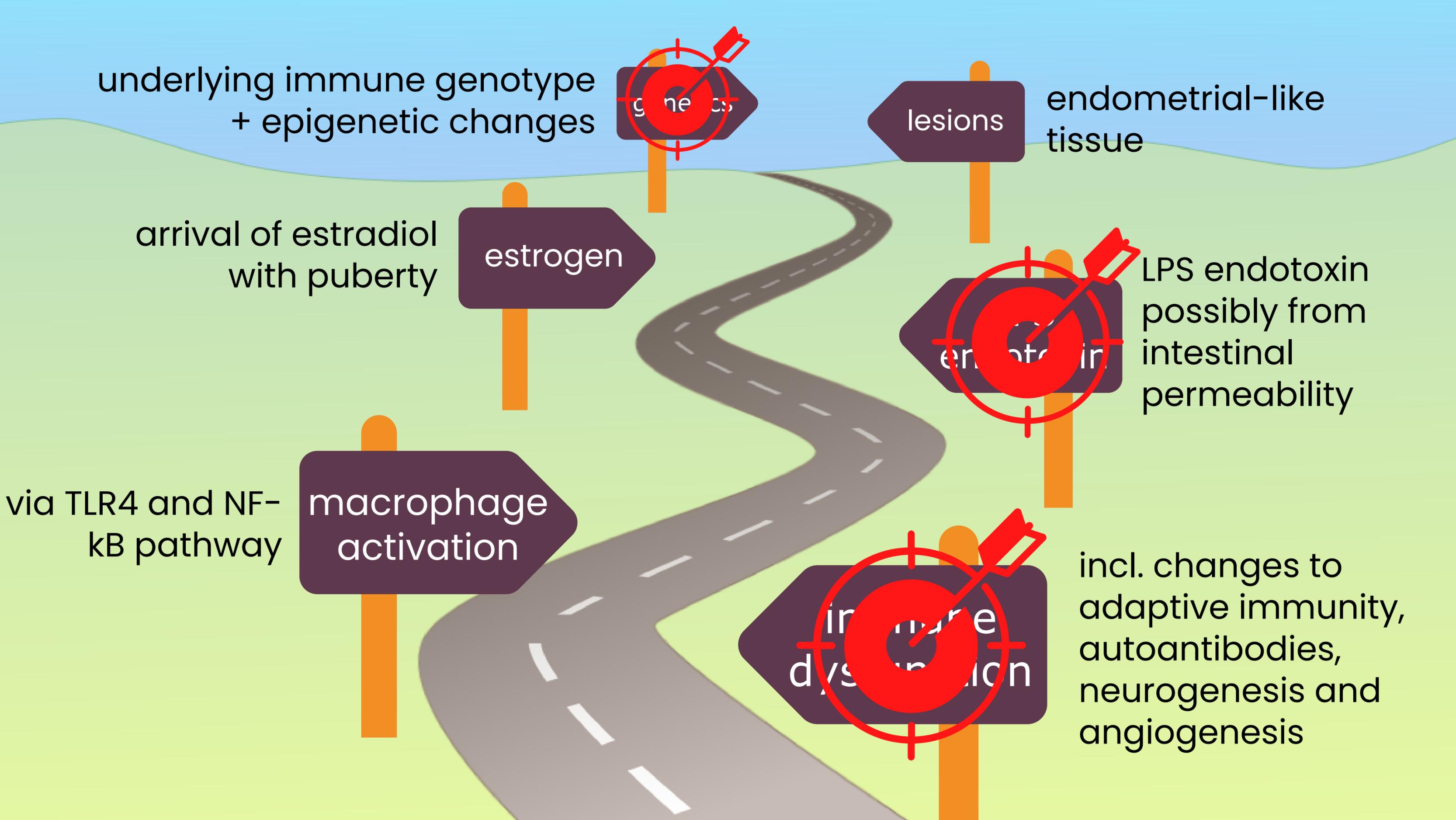


Crosstalk between Innate Immunity and Adaptive Immunity











Autoimmune genotype

- Strict avoidance of gluten. Sturgeon and Fasano 2016.. Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases
- Strict avoidance of AI casein and maybe eggs.

REVIEW

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

Craig Sturgeon^{a,b} and Alessio Fasano^{a,c}

^aCenter for Celiac Research and Treatment, Mucosal Immunology and Biology Research Center, Massachusetts General Hospital and Division of Pediatric Gastroenterology and Nutrition, Boston, MA, USA; ^bGraduate Program in Life Sciences, University of Maryland School of Medicine, Baltimore, MD, USA; ^cEuropean Biomedical Research Institute of Salerno (EBRIS), Salerno, Italy



LPS toxin

- **Antibiotic treatment.** Khan et al. 2021. Levofloxacin or gonadotropin releasing hormone agonist treatment decreases intrauterine microbial colonization in human endometriosis.
- **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.

[Exp Ther Med.](#) 2017 Dec; 14(6): 6125–6130.

Published online 2017 Oct 16. doi: [10.3892/etm.2017.5316](https://doi.org/10.3892/etm.2017.5316)

PMCID: PMC5740511

PMID: [29285168](https://pubmed.ncbi.nlm.nih.gov/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
- retinol
- selenium
- N-acetyl cysteine
- vitamin D
- curcumin
- resveratrol
- medicinal cannabis

Messalli et al. 2014. The possible role of zinc in the etiopathogenesis of endometriosis.

Barra et al. 2018. The use of retinoic acid for the treatment of endometriosis.

Chen et al. 2020. Selenium alleviates lipopolysaccharide-induced endometritis.

Porpora et al. 2013. A promise in the treatment of endometriosis.

Kalaitzopoulos et al. 2020. Association between vitamin D and endometriosis.

Vallée et al. 2020. Curcumin and endometriosis.

Dull et al. 2019. Therapeutic approaches of resveratrol on endometriosis.

Sinclair et al. 2021. Effects of cannabis ingestion on endometriosis.

- **iodine** (1-3 mg) but only if thyroid antibodies are NOT detectable



Review

Immunology and Immunotherapy of Endometriosis

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- * Correspondence: radoslaw.maksym@cmkp.edu.pl

— “ —
Lipiodol (ethiodized oil) inhibits peritoneal lymphocyte and macrophage activity and upregulates NK, dendritic, and Treg cells.
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Abstract: Endometriosis is one of the most common gynecological and systemic diseases, with a remarkable immune background. Patients suffer from pain and fertility reduction. Due to the distinct immune component, an immunotherapeutic approach may gain importance in the future.

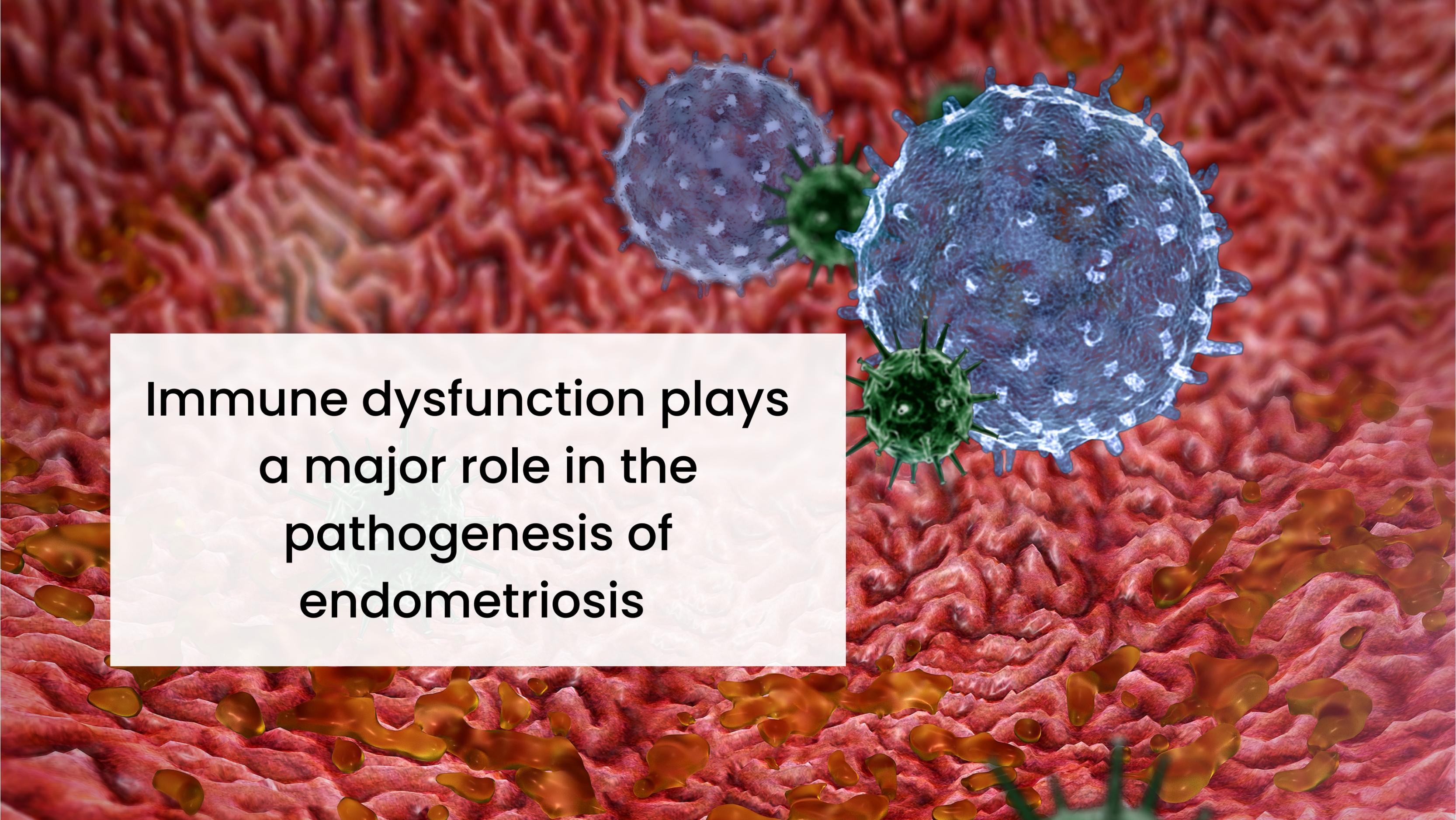
Other considerations



- 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**

A 3D medical illustration showing a cross-section of tissue. The background is a dense, textured surface of reddish-pink cells. In the foreground, there are several large, blue, spherical cells with spiky protrusions, likely representing macrophages or dendritic cells. Two smaller, green, spherical cells with spiky protrusions, likely representing pathogens or viruses, are shown interacting with the blue cells. The overall scene suggests an immune response or infection within the tissue.

**Immune dysfunction plays
a major role in the
pathogenesis of
endometriosis**

A close-up photograph of a person's hands, with fingers interlaced to form a heart shape over their midsection. The person is wearing a teal-colored t-shirt. The background is a soft, out-of-focus gradient of light blue and white.

**Look to the gut and
LPS endotoxin**

The image features a top-down view of several magnifying glasses with silver handles and frames, scattered across a bright yellow background. The handles are black and have a textured grip. The lenses are clear and reflect the yellow background. A white rectangular box is centered over the image, containing the text.

**Consider gluten and other
immune disruptors**

**Nourish and support a
healthy immune and
nervous system**

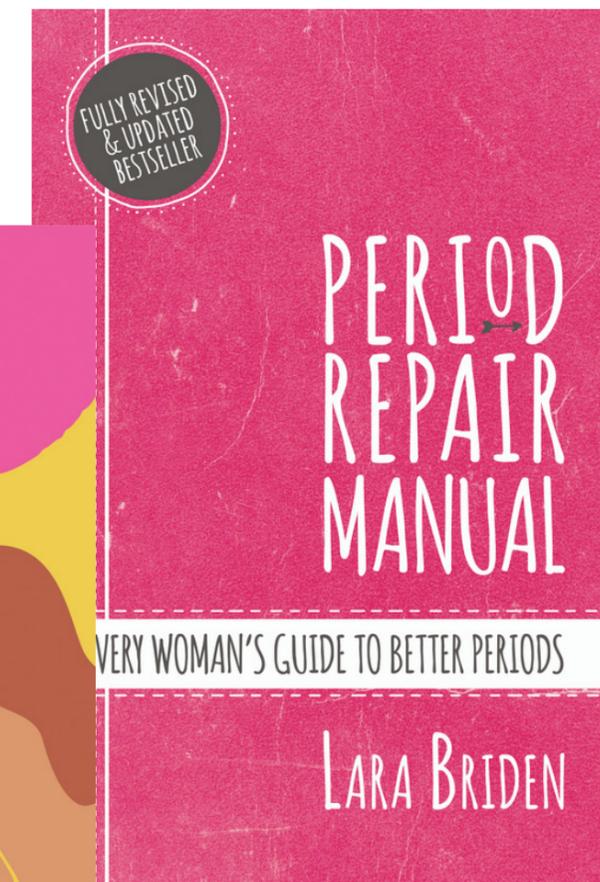
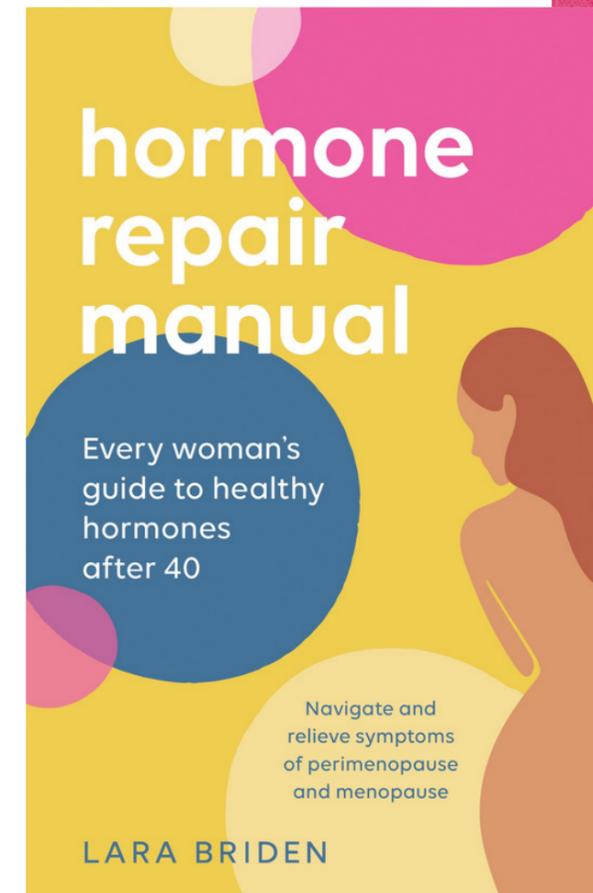


Questions?

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