PROBIOTICS IN RHEUMATOLOGIC DISEASE

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Rheumatologic disease

- Chronic inflammatory autoimmune disorders, can affect multiple organs
- Likely causes of the onset or development:
  - Genetic,
  - sex-specific variables,
  - diet,
  - oral health
  - gut microbiota imbalance
- ***the specific pathways remain unknown***

Gut homeostasis

- interaction between the host immune system and commensal microbiota
- enhanced gut permeation due to gastrointestinal (GI) tract inflammation → food antigens and dangerous microorganisms to travel through the blood → Antibodies to antigens → immunological complex in the joint and…
- In most rheumatologic disease gut microbiota is affected
- link between the microbiome and immune-mediated diseases → Gut bacteria may play a role in the development of arthritis →

Gut microbiota and immune system

- The mode of delivery and mode of feeding in the first years of life: *establishment of gut microbiota, may affect the development of autoimmune diseases.*
- Gut microbiota is required for normal immune system maturation, including gut-associated lymphoid tissue development: *tolerance induction to autoantigens* in the gut mucosa:

❑ *GF mice :*

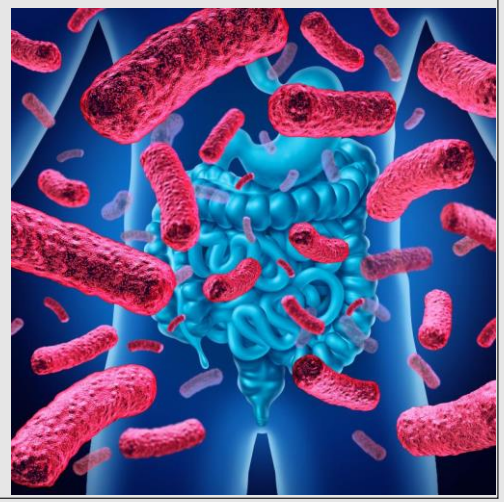
✓ showed decreased numbers of CD4+ T cells,

✓ secreting IgA plasma cells and antimicrobial peptides,

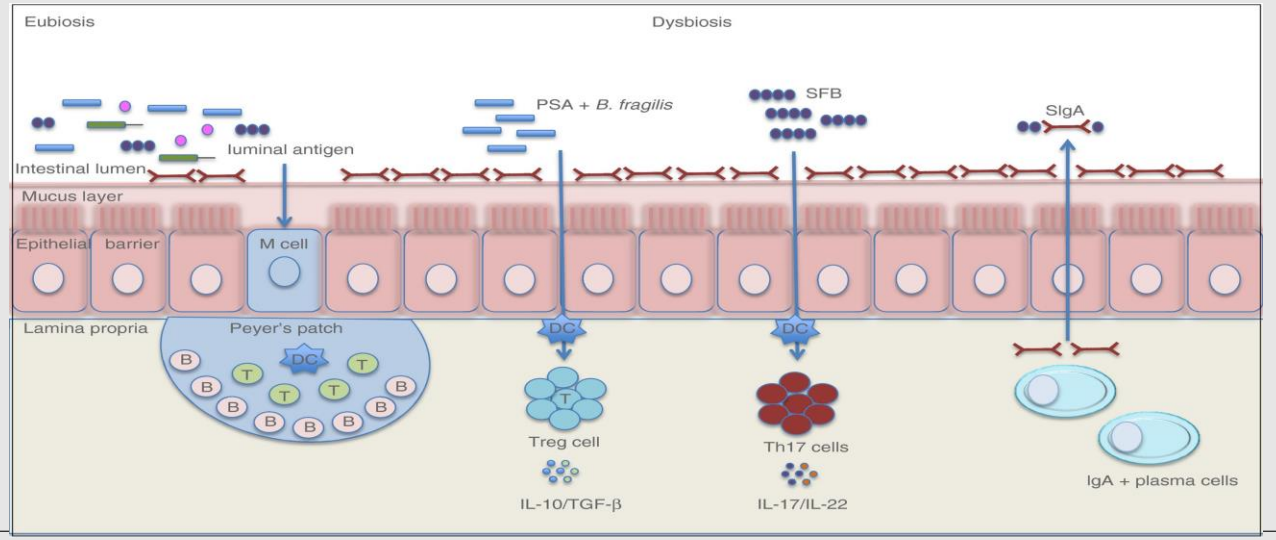
✓ a thinner mucus layer and Peyer's patches

✓ The spleen and lymph nodes are abnormally developed,

✓ decreased numbers of B and T cells in the germinal centers



- The resident microbiota regulates the development of *specific subsets* of lymphocytes in the gut.
- *T helper type 17* (Th17) lymphocytes and their accumulation in the intestine,
- *Regulatory T (Treg) cells*: maintenance of homeostasis, Treg cell depletion : an abnormal expansion of CD4+ T cells, resulting in *gut inflammation*.
- *IgA-secreting plasma cells*



Gut microbiota and autoimmune disease

❖ ***Intestinal dysbiosis observed in autoimmune diseases is associated with*:**

✓ decreased bacterial function and diversity,

✓ impaired gut barrier function,

✓ increased inflammation

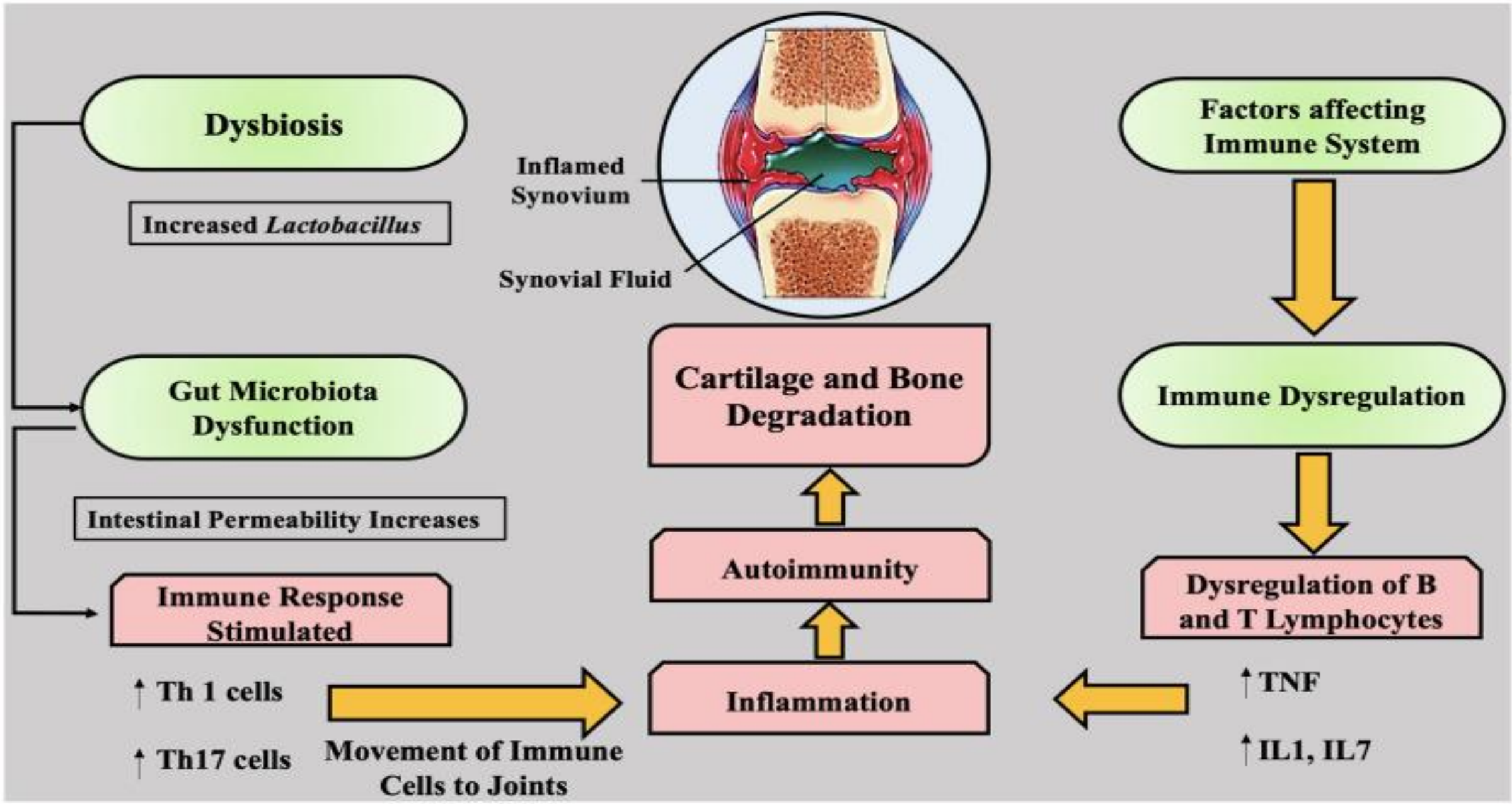
✓ and decreased Treg cells in the gut

❖ ***hypotheses* :**

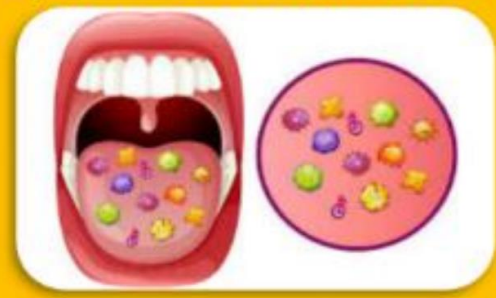
➢ molecular mimicry

➢ post-translational modification of luminal proteins

➢ toxemic factor


Dysbiosis
Increased *Lactobacillus*
Gut Microbiota Dysfunction
Intestinal Permeability Increases
Immune Response Stimulated
↑ Th 1 cells
↑ Th17 cells
Movement of Immune Cells to Joints
Inflamed Synovium
Synovial Fluid
Cartilage and Bone Degradation
Autoimmunity
Inflammation
Factors affecting Immune System
Immune Dysregulation
Dysregulation of B and T Lymphocytes
↑ TNF
↑ IL1, IL7

The dysbiosis of **oral microbiome**



caused by the diet, host's environment, smoking and genetic susceptibility

contribute to the pathogenesis of

Rheumatoid arthritis, **Sjögren's syndrome** and **Systemic lupus erythematosus**

Rheumatoid arthritis.

Changes in the gut and oral microbiomes may contribute to the pathogenesis of RA. An altered oral microbiome has been identified in patients with early RA. *P. gingivalis* is strongly linked in pathogenesis

Sjögren's syndrome.

A dysregulated immune response against the normal oral microbiome can be responsible for SS pathogenesis

Systemic lupus erythematosus.

The local oral microenvironment may participate in the development of SLE through developed autoantibodies against oral microbial products

Rheumatoid arthritis

- a systemic autoimmune disorder characterized by chronic inflammation of multiple joints, bone erosion and cartilage destruction
- *interaction of HLA genes and environmental factors*, such as smoking and infections
- *dysbiosis* has been identified as a possible trigger factor
- animal models :
- administration of antibiotics exacerbates the disease and increases the level of IL-6, IFN-c and IL-17 pro-inflammatory cytokines

Recent studies

- gut microbiota of the genetically arthritis-susceptible transgenic mice and in the genetically resistant transgenic mice:
- *Clostridia* were prevalent in susceptible mice, whereas the *Porphyromonadaceae* and *Bifidobacteriaceae* families were dominant in resistant mice
- increased *intestinal permeability* and a *Th17 profile* in susceptible mice,
- gut microbiota transplant *induced an increase in the number of Th17 cells in the gut and severe arthritis.*

- Increase in *Lactobacillus salivarius*, *Lactobacillus iners* ,*Lactobacillus ruminis*, *Eggerthella, Actinomyces,Turibacter, Streptococcus* and *Collinsela* reads in the gut microbiota of people with RA, with positive correlations with the pro-inflammatory cytokine IL-17

Systemic lupus erythematosus

- an autoimmune and heterogeneous disease characterized by damage to the skin, kidneys, lungs, joints, heart and brain.
- pathogenesis of SLE may involve :
- genetic and environmental factors, such as viral infections,
- defective apoptosis and
- solar exposure to ultraviolet-B waves.
- *increased evidence has emerged that suggests the role of intestinal dysbiosis in SLE development.*

Recent studies

- ✓ decrease in the relative abundance of *Lactobacillus spp* and an increase in *Lachnospiraceae* members when compared with controls.
- ✓ *dietary intervention*, caloric restriction, in mice :changes in the gut microbiota and *avoided disease progression*
- ✓ given drinking water with a *low pH* have altered gut microbiota and *decreased antinuclear antibodies*, and develop nephritis more slowly,
- ✓ suggesting that gut microbiota modulation might influence disease progression.
- ✓ *GF lymphotoxin-deficient mice, intestinal microbiota could play a role in antinuclear antibody induction and IL-17 receptor signaling.*

- *decreased Firmicutes* : Bacteroidetes ratios in the patients with SLE.
- intestinal dysbiosis observed in patients with SLE could be linked to an *increase in oxidative phosphorylation*
- *mouse models of SLE* :probiotic supplementation ameliorates disease activity, Treg regulation, and typical comorbidities like cardiovascular complications
- lactobacilli administration appeared to delay SLE progression via mechanisms involving Treg induction and IL-10 production:

❖ *supporting the use of these strains as therapeutic probiotics for autoimmune diseases.*

Spondyloarthritis

- psoriatic arthritis and ankylosing spondylitis
- dysbiosis might represent an important risk factor in these diseases
- patients with SpA often have signs of bowel disease.
- probiotics could strengthen the epithelial barrier and modulate intestinal microbiota

❑ *Only an RCT* :A probiotic combination in active ankylosing spondylitis (over a period of 12 weeks):

➢ did not demonstrate significant benefit

❑ *A pilot non-controlled study*:18 patients with SpA associated with ulcerative colitis:

➢ a combination of L. acidophilus and L. salivarius ameliorate SpA through a reduction in disease activity and patients' perception of pain

Systemic sclerosis

❖ chronic disease of unknown cause :diffuse fibrosis and vascular abnormalities in the skin, joints, and internal organs

❑ some RCTs (in patients with gastrointestinal involvement):

➢ 8-week probiotics supplementation did not have any effect in reducing gastrointestinal symptoms but lead to a decrease in Th17 cell level

❑ Another trial :

➢ confirmed the inefficacy of probiotics in systemic sclerosis associated gastrointestinal disease

Sjogren's syndrome

- chronic autoimmune disease characterized by oral and ocular dryness
- individuals with dry eye had gut microbiome alterations as compared to healthy controls
- Recently, there has been an interest in understanding interactions between gut bacteria and mucosal immunity in a number of eye diseases including Sjogren's
- a few studies in Sjogren patient:
- significant differences between case and control gut microbiota
- several bacterial classes correlated with dry eye symptoms and signs

Probiotic applications in rheumatologic diseases

- Studies suggest that probiotics:
- *influence systemic immune responses*,
- *ensure the homeostasis of the healthy microbiota* in the intestinal mucosa and
- could, therefore, be used as *adjuvant therapy* to treat immune-mediated diseases.

MECHANISMS OF ACTION

- The possible mechanism of action:

- ✓ mucus secretion,
- ✓ antimicrobial peptide production,
- ✓ the maintenance of the function of the gastrointestinal–epithelial barrier,
- ✓ ensuring adequate interactions between the gut microbiota and the mucosal immune cells
- ✓ helping the activation of the host immune system in response to pathobionts

- ❖ the mechanisms of systemic anti-inflammatory and immunomodulating are *still largely unclear*
- ❖ in vitro animal models: short chain fatty acids metabolites. (butyrate, acetate, and propionate)
  - ➢ regulation of different immune cell functions (impact on peripheral immune response)
- ❖ **Butyrate** has demonstrated to suppress antigen-induced arthritis in mice by :
  - ➢ affecting both B and T cell development.
  - ➢ it inhibits germinal center B cell and plasmablast differentiation and cytokine production by invariant NKT cells

- RA patients: increase polarization toward a T regulatory (Treg) phenotype with a decrease in Th17 cell
- conversion of T cells into Tregs expressing
- modulation of TLR signaling: ability in binding specific TLRs
- Other mechanisms: activation of adenosine receptors by specific probiotic stains: suppressive effect of Treg

Recent studies

- In a recent study, the oral administration of Bacillus coagulans, which has an anti-inflammatory effect:

✓ promoted a decrease in the level of serum amyloid A protein and tumor necrosis factor serum in rat models of RA.

- a double-blind, placebo-controlled trial:

✓ improvement in disease activity score, increased levels of serum IL-10, and decreased levels of tumor necrosis factor, IL-6 and IL-12 in treated patients

- Another clinical trial: evaluated the administration of Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium bifidum for 8 weeks in 60 RA patients:

✓ Probiotic intake improved DAS28, decreased the level of serum C-reactive protein

- In a lupus-like animal model, the administration of retinoic acid :
  - restored Lactobacillus spp
  - and improved lupus symptoms

- Some Lactobacillus species :have immunomodulatory properties in the host gut mucosa:
  - inhibiting neutrophil extracellular trap formation,
  - improving antioxidant status and
  - increasing the expression of adhesion molecules in the gut

At the end...

- Emerging findings associate intestinal dysbiosis with autoimmune disease pathogenesis
- Mucosal surfaces with impaired microbiota function and diversity: trigger site of autoimmunity
- lifestyle, and mainly diet, can influence chronic disease course and pathogenesis
- dietary control and supplementation might support standard treatments.
- results of the RCTs limited to firmly conclude their effect in improving disease activity or progression
- However, their promising anti-inflammatory and immunomodulating properties are worth


THANK YOU