Intestinal permeability (IP): breaking the vicious cycle

fx Medicine® BioCeuticals

Your **INTESTINAL SURFACE AREA** spans **400m²**[1,2]
(about the size of a full basketball court)

INCREASED IP refers to the **loss of integrity** of the **intestinal cell barrier**[1,3]

Increased IP allows **LARGER MOLECULES AND TOXINS** to enter circulation and trigger **immune** or **inflammatory responses**[4-6]

WOMEN can have **HIGHER IP** than **MEN** **(influenced by sex hormones** and the **microgenderome)**[7-9]

KEY CONTRIBUTORS

- Chronic inflammatory diseases e.g. coeliac disease (CD), inflammatory bowel disease (IBD)
- Gut infections and dysbiosis
- Dietary factors (high fat, high sugar)
- Alcohol consumption
- Medications e.g. nonsteroidal anti-inflammatory drugs, antibiotics
- Chemicals e.g. advanced glycation end products, microplastics
- Smoking/vaping tobacco
- Chronic stress
- Inadequate or excessive physical activity
- Food allergies or sensitivities[2,4-6,10,11]

ASSOCIATED CONDITIONS

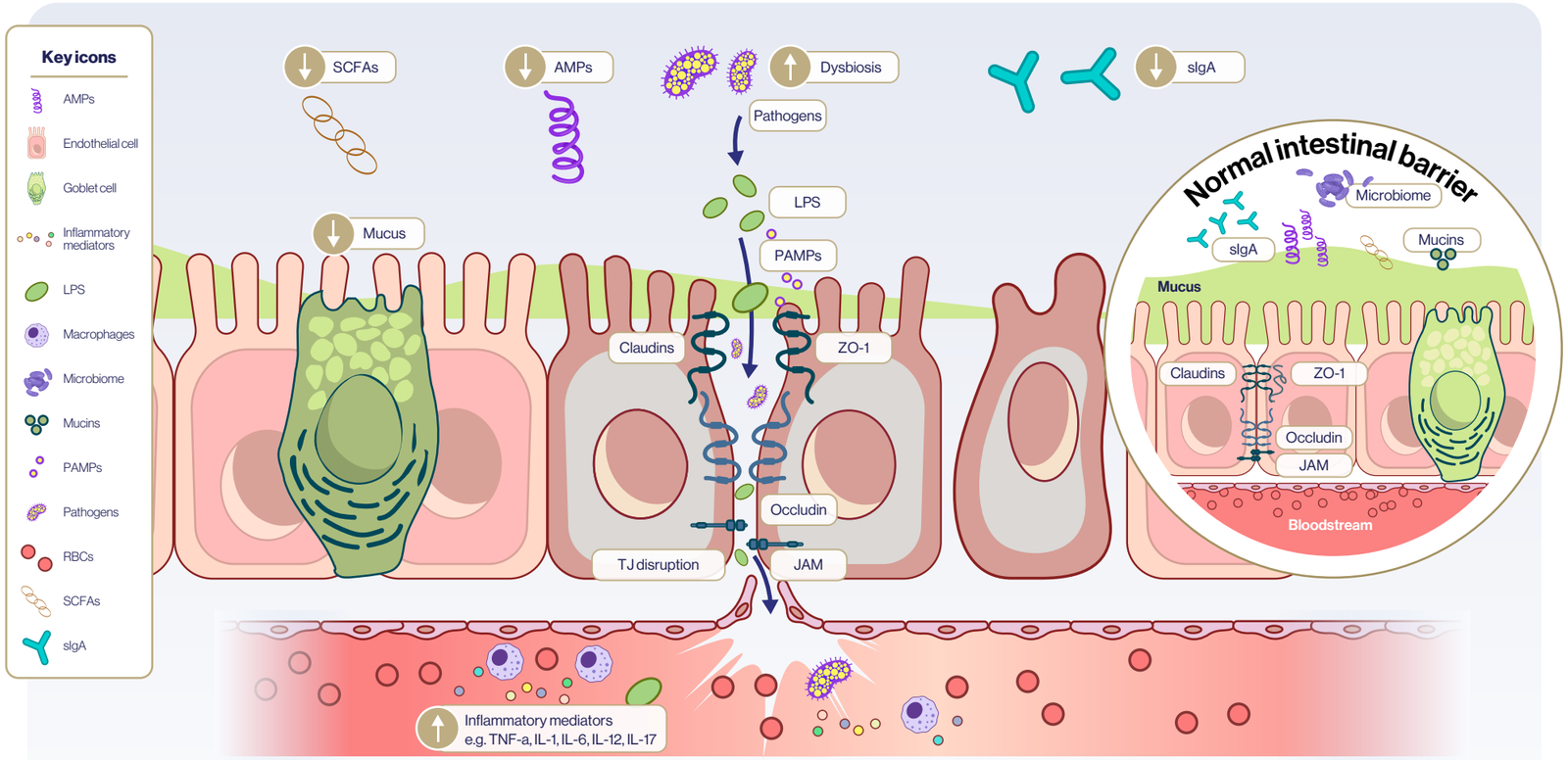
Increased IP is associated with the development and/or progression of many metabolic, autoimmune, and systemic conditions, including:

- Gastrointestinal conditions e.g IBD, CD, imitable bowel syndrome (IBS)
- Obesity and metabolic syndrome
- Liver diseases e.g. cirrhosis
- Allergies, hypersensitivities and asthma
- Type 1 and type 2 diabetes
- Atherosclerosis and cardiovascular diseases
- Polycystic ovary syndrome
- Alzheimer's and Parkinson's disease
- Autism spectrum and mood disorders
- Skin complaints e.g. psoriasis
- Arthritis and rheumatologic diseases[1-6,8,10-12]

KEY

AMPs: antimicrobial peptides; **GPx**: glutathione peroxidase; **Ig**: immunoglobulin; **IL**: interleukin; **IP**: intestinal permeability; **JAM**: junctional adhesion molecule; **LPS**: lipopolysaccharide; **MPO**: myeloperoxidase; **NF-α** : nuclear factor-alpha; **NF-kB**: nuclear factor-kappa B; **Nrf2**: nuclear factor erythroid 2-related factor 2; **PAMPs**: pathogen-associated molecular patterns; **PGE2**: prostaglandin E2; **RBC**: red blood cells; **ROS**: reactive oxygen species; **SCFA**: short chain fatty acids; **sIgA**: secretory IgA; **SOD**: superoxide dismutase; **TGF-β**: transforming growth factor-beta; **Th17**: T helper 17 cell; **TJ**: tight junctions; **TNF-α**: tumour necrosis factor-alpha; **Treg**: regulatory T cell; **ZO-1**: zonula occludens-1

Increased IP pathophysiology and therapeutic interventions[1-14]



Reduced sIgA levels: (L)
- Weakens first line intestinal immune defence
- Allows microbes and toxins to adhere to intestinal wall
- Contributes to dysbiosis and translocation of antigens across the epithelial barrier
- Increases inflammation (sIgA neutralises pro-inflammatory antigens)

Decreased SCFA production (C G L M)
Insufficient SCFAs leads to:
- Inadequate energy source to maintain enterocyte structure and function
- Disrupted expression of TJ proteins (e.g. ZO-1, occludin, claudin) causing epithelial damage
- Reduced mucus production (depleting the first physical barrier)
- Increased translocation of bacterial products like PAMPs

Gut microbiota dysbiosis (C G L M)
Imbalances in gut microbiota composition:
- Reduces SCFA production
- Increases LPS
- Triggers inflammation
- Pathogens directly disrupt TJ proteins

Disruption of TJ proteins (C G GSH L M)
Altered expression or function of TJ proteins
- Weakens the paracellular barrier
- Allows antigens and microbes to pass through the epithelium

Translocation of antigens (C G GSH L M)
IP allows translocation of pathogens, LPS and undigested food particles into the bloodstream, leading to endotoxemia and systemic low-grade inflammation

Increased immune activation (C G GSH L M)
Immune activation and release of pro-inflammatory mediators disrupts TJs and compromises epithelial barrier integrity

Oxidative stress and epithelial injury (C G GSH L M)
Oxidative stress and imbalanced enterocyte proliferation/ apoptosis lead to barrier dysfunction and increased IP

THERAPEUTICS

C Curcumin (Theracurmin®)
Anti-inflammatory, immunomodulator, antioxidant
- Strengthens tight junction proteins (e.g. ZO-1)
- Reduces inflammation and oxidative stress
- Regulates gut immunity (e.g. Th17/Treg balance)
- Increases SCFA production (e.g. butyrate)
- Biofilm disruptor and antimicrobial
- Improves gut microbiome composition
- Stimulates gastric secretions (e.g. mucin)[54-66]

G Glutamine
Anti-inflammatory, antioxidant, nutritive
- Fuel for enterocytes and immune cells
- Reduces NF-κB and pro-inflammatory cytokines (e.g. IL-6 and IL-8)
- Strengthens tight junctions and decreases zonulin
- Enhances SOD and oxidative status
- Improves abundance and diversity of gut microbiota (including SCFA producers)
- Increases immunoglobulin (Ig) defence antigens IgG and IgM[13-23]

GSH Glutathione
Antioxidant, anti-inflammatory, gastroprotective
- Enhances tight junction and mucin expression
- Improves mitochondrial function; reduces ROS
- Detoxifies harmful substances (e.g. xenobiotics)
- Lowers inflammatory mediators and reduces mast cell recruitment[35-45,67]

L Licorice root (GutGard®)
Gastroprotective, antimicrobial, anti-inflammatory
- Enhances tight junction protein expression (claudins, occludin, ZO-1, JAM)
- Reduces inflammatory cytokines
- Increases sIgA and anti-inflammatory IL-10
- Improves intestinal microbiome
- Decreases oxidative stress[24-34]

M Chios mastic gum (*Pistacia lentiscus*)
Mucoprotective, anti-inflammatory, prebiotic, antioxidant
- Upregulates tight junction proteins (ZO-1)
- Enhances gut microbiota composition
- Regulates immune function (e.g. Th17 cells)
- Inhibits pro-inflammatory cytokines (e.g. TNF-α)
- Reduces inflammation and activates Nrf2 pathway[46-53]

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