

# HOW FOOD INTOLERANCES CAUSE INFLAMMATION

Here's a clear, science-grounded map of how “intolerant” foods can amplify gut and body inflammation—without assuming a classic IgE allergy. Think of it as four overlapping pathways: **mechanical/osmotic stress**, **barrier breakdown**, **microbiome-immune signaling**, and **biogenic amine/mast-cell activation**. I'll name the key molecules and receptors so you can trace each step.

## 1) Malabsorption → Osmotic load & fermentation stress

**Who:** lactose, excess fructose, FODMAPs, sugar alcohols; also starches reaching the colon fast.

**What happens**

- **Osmosis:** Unabsorbed carbs pull water into the lumen → distension → epithelial stress.
- **Fermentation:** Microbes convert them to **gases** (H<sub>2</sub>, CO<sub>2</sub>, CH<sub>4</sub>) + **organic acids** (lactate, acetate, propionate, butyrate).
  - Rapid fermentation spikes **luminal acidity** and pressure; stretching activates **TRPV** and **mechanosensitive** pathways on epithelial and immune cells.
- **Immune nudge:** Distension and acidification can trigger **epithelial IL-33/TSLP** release (alarm signals) and amplify **NF-κB** in stressed enterocytes.

**Net effect:** more permeability and “danger” cues that prime the mucosal immune system—even if calprotectin stays modest.

## 2) Barrier dysfunction (“leaky gut”) & epithelial signaling

**Who:** gluten/gliadin (in some), **amylase–trypsin inhibitors (ATIs)** in wheat, alcohol, bile acids in the wrong place, some additives (emulsifiers), stress.

**What happens**

- **Tight junction opening:**
  - **Zonulin pathway**—gliadin can bind **CXCR3** on enterocytes → zonulin release → **occludin/cludin** reorganization → higher paracellular permeability.
  - **Cytokine-driven**—TNF-α, IL-13, and oxidative stress also loosen junctions.

- **Bile acids out of place:** Ileal malabsorption sends bile acids to the colon → activate **TGR5/FXR** and can directly irritate epithelium, increasing permeability and water secretion.
- **Emulsifiers (e.g., CMC, polysorbate-80):** thin the **mucus layer**, allowing **bacterial encroachment** toward the epithelium.

#### Immune result

- More **microbial products** (LPS, flagellin, peptidoglycan) and food fragments cross the fence → engage **TLR4/TLR5/NOD** on epithelial cells, dendritic cells, and macrophages → **MyD88** → **NF-κB** → **IL-1β, IL-6, TNF-α**.
- Enterocytes under stress release **IL-8** (neutrophil chemotaxis) and **alarmins** (IL-33).

### 3) Microbiome shifts (dysbiosis) → innate immune activation

**Who:** repeatedly irritating foods for *you*, ultra-processed/high-fat meals (with endotoxin carriage), low fiber, SIBO.

#### What happens

- **Community change:** Less **butyrate-producers** (e.g., *Faecalibacterium prausnitzii*) and more pathobionts (e.g., **Enterobacteriaceae**) → fewer **HDAC-inhibiting** anti-inflammatory SCFAs (notably **butyrate**).
- **Lower butyrate** weakens epithelial energy supply and **tight junction gene expression**; butyrate normally promotes **Treg** via **GPR109A** and epigenetic effects. Lose that, lose tolerance.
- **Metabolic endotoxemia:** Dietary fat can ferry **LPS** into chylomicrons → mild, transient **TLR4** activation systemically; if the barrier is compromised, the signal is stronger.
- **NLRP3 inflammasome:** Cellular stress (ROS, uric acid from high fructose loads, ATP, ion flux) activates **NLRP3** → **caspase-1** → **IL-1β/IL-18** maturation.

**Result:** Innate immune tone rises; adaptive responses (Th1/Th17) are easier to trigger in susceptible hosts (e.g., Crohn's).

### 4) Biogenic amines & mast-cell axis (histamine pathway)

**Who:** “high-histamine” or histamine-liberating foods (aged cheeses, wine, cured meats, certain fish), **DAO** deficiency/overload, some FODMAPs that promote histamine-producing microbes.

## What happens

- **Histamine excess** (poor degradation by **diamine oxidase—DAO**) or **mast-cell degranulation** in the mucosa → activation of **H1/H2/H4 receptors** on nerves, vessels, and immune cells.
- Mast-cell mediators (**histamine, tryptase, prostaglandins, leukotrienes**) increase **vascular permeability**, stimulate nerves (pain/urgency), and recruit leukocytes.
- Histamine also modulates dendritic cells and T-cell polarization, sustaining local inflammation.

**Result:** “Food makes me flush/bloat/urgent” pattern, often worse with stress (CRH can prime mast cells).

## 5) Non-IgE immune responses (distinct from classic allergy)

- **T-cell-mediated or innate responses** to food components (e.g., **ATIs** in wheat activate **TLR4** on myeloid cells; **glycated proteins/AGEs** from high-fructose, high-heat foods can trigger **RAGE** and oxidative stress).
- **IgG/IgG4** food antibodies are **not** reliable markers of intolerance; they often reflect exposure/tolerance, but in a leaky, inflamed gut they may correlate with symptoms because of barrier breach—not because they’re causal.

## 6) Degree of Symptoms

These pathways are **context-dependent**:

- A resilient **mucus + tight junction** barrier, **butyrate-rich microbiome**, good **DAO** activity, and low **baseline cytokines** = less symptoms.
- A flared or stressed gut flips the same exposures into **distension + barrier leak + innate signaling**, tipping you into overt symptoms.

## Putting the biochemistry into practice (action steps)

1. **Reduce triggers while you heal the barrier**
  - Short **low-FODMAP** phase → less fermentation pressure.
  - If ileal disease/rapid transit: manage **bile acids** (dietary fat timing, ox-bile or bile-acid binders under guidance).
2. **Rebuild the barrier & tolerance**
  - **Butyrate sources:** soluble fiber (oats/psyllium/chia) as tolerated; consider **butyrate supplements**.
  - **Polyphenols** (berries, olive oil) support **AHR/Treg** pathways and antioxidant tone.
  - **Sleep & stress:** cortisol/CRH affect tight junctions and mast cells—improving sleep measurably **lowers CRP**.
3. **Tame histamine if it’s your pattern**

- Trial a **low-histamine** rotation; support **DAO** with micronutrients (B6, copper, vitamin C); stabilize mast cells with **quercetin/luteolin** (if tolerated).
- 4. **Support anti-inflammatory signaling**
  - **Omega-3 (EPA/DHA)** tilt eicosanoids toward **resolvins/protectins**; **curcumin** inhibits **NF-κB**; **vitamin D** nudges toward **tolerance/Treg**.
- 5. **Reintroduce foods methodically**
  - Add back **one FODMAP class at a time**, increasing dose across 3 days; watch for **dose-dependent** thresholds (classic for carbohydrate malabsorption).

## One-page pathway summary (at a glance)

- **Carb malabsorption** → osmotic water + fast fermentation → distension/acid → epithelial stress (IL-33/TSLP) → **innate priming**.
- **Barrier opening (zonulin, cytokines, bile acids, emulsifiers)** → microbial MAMPs cross → **TLR/NOD** → **NF-κB** → TNF-α, IL-6, IL-1β.
- **Dysbiosis/low butyrate** → fewer Tregs, weaker junctions → **NLRP3** easier to trigger.
- **Histamine/mast cells** → H1/H2/H4 signaling → permeability, pain, leukocyte traffic.
- **High-fat “endotoxin ride” & fructose** → LPS via chylomicrons; hepatic **uric acid** → **NLRP3**.