From Leaky Gut to Anabolic Resistance: How Your Microbiome Determines Your Gains

When your intestinal barrier is compromised, the downstream affects are significant that if left unchecked will inevitable cause disease. Lipopolysaccharide (LPS) translocates in the bloodstream, activating NF-κB and elevating pro-inflammatory cytokines (TNF-α, IL-6) (Mishra et al., 2025). These signals impair insulin sensitivity and blunts mTOR activation, creating a state of anabolic resistance (Ji et al., 2025). Even in young, healthy athletes, chronic dysbiosis and leaky gut can significantly reduce the anabolic response to protein intake, meaning you are leaving potential gains on the table despite perfect nutrition.(Aragon et al., 2020). In Ji et al. (2025), several mechanisms are described through which a leaky gut contributes to the development of insulin resistance. One key mechanism involves the translocation of lipopolysaccharide (LPS) from the intestinal lumen into systemic circulation. This process and its downstream molecular effects are summarized in **Table 1** below.

Table 1. Microbial Modulation of the IRS-1 → PI3K → Akt → mTOR Pathway

Microbial Factor	Primary Cellular Target	Pathway Impact on IRS-1 → PI3K → Akt → mTOR Cascade	Consequence
Lipopolysaccharide (LPS)	**TLR4 on skeletal muscle, liver, and adipose cells**	LPS binds to TLR4, activating NF-κB and JNK signaling, which phosphorylate IRS-1 on serine residues. This prevents IRS-1 from transmitting the insulin signal to PI3K, blocking the sequential activation of Akt and mTORC1.	Insulin resistance: impaired glucose uptake, reduced glycogen synthesis, and suppression of mTOR-driven protein synthesis (anabolic resistance).
Leucine (Nutrient Bypass Mechanism)	**Sestrin2 / Leucyl-tRNA synthetase (LRS) → Rag GTPases → mTORC1**	Leucine directly activates mTORC1 independent of insulin, IRS-1, or Akt, by binding Sestrin2 and LRS to trigger Rag GTPase-mediated recruitment of mTORC1 to the lysosomal membrane.	Restored anabolic signaling: promotes protein synthesis and muscle maintenance despite impaired insulin signaling.

The Intestinal Barrier: Your First Line of Defense

The intestinal epithelium forms a permeable barrier that regulates nutrient absorption while preventing harmful substances from entering systemic circulation (Pérez-Reytor et al., 2021). This barrier integrity depends on tight junction proteins including claudin-1, occludin, and zonula occludens-1 (ZO-1) that seal the paracellular space between epithelial cells (Pérez-Reytor et al., 2021).

A healthy gut microbiota maintains this barrier by producing short-chain fatty acids (SCFAs), particularly butyrate, which serves as the primary energy source for colonocytes and enhances tight junction assembly (Wang et al., 2023; Pérez-Reytor et al., 2021). However, when dysbiosis disrupts this delicate ecosystem, the consequences are immediate and severe. Reduced abundance of beneficial SCFA-producing bacteria like *Faecalibacterium prausnitzii* and *Bifidobacterium* compromises barrier function (Mishra et al., 2025).

Concurrent expansion of pro-inflammatory, LPS-enriched microbes, particularly Proteobacteria, increases the luminal burden of endotoxin (Mishra et al., 2025). This dysbiotic shift activates protease-activated receptors and protein kinase C pathways that phosphorylate and disrupt tight junction proteins, leading to increased intestinal permeability (Pérez-Reytor et al., 2021; Ghosh, 2021).

LPS Translocation: The Inflammatory Cascade

Once the barrier is breached, LPS translocates from the gut lumen into the lamina propria and portal circulation, a phenomenon termed metabolic endotoxemia (Pérez-Reytor et al., 2021). Studies demonstrate antibiotic-induced dysbiosis independently elevates circulating endotoxin (Cani, 2007). LPS binding to Toll-like receptor 4 (TLR4) on immune cells and intestinal epithelium triggers MyD88-dependent signaling cascades that activate NF-κB transcription factors, initiating a pro-inflammatory storm characterized by elevated TNF-α, IL-1β, and IL-6. (Pérez-Reytor et al., 2021).

This activation initiates a pro-inflammatory storm characterized by elevated TNF-α, IL-1β, IL-6, and IL-8 (Pérez-Reytor et al., 2021). Experimental models confirm that inhibiting TLR4 signaling or restoring barrier integrity reduces systemic inflammation and improves insulin sensitivity (Pérez-

Reytor et al., 2021; Calder, 2021). The chronic low-grade inflammation driven by LPS not only impairs metabolic homeostasis but also creates a catabolic environment directly antagonistic to muscle growth.

From Inflammation to Anabolic Resistance

The concept of anabolic resistance describes the blunted muscle protein synthesis response to protein ingestion and resistance exercise (Aragon et al., 2020). This phenomenon is particularly pronounced in aging but can affect individuals of any age when inflammatory burden is high (Aragon et al., 2020). The inflammatory cytokines TNF-α and IL-6 directly impair insulin signaling by promoting serine phosphorylation of insulin receptor substrate-1 (IRS-1), which inhibits downstream PI3K/Akt pathway activation (Mishra et al., 2025; Calabrò et al., 2023; Ji, 2025)

This signaling disruption has profound consequences for mTOR activation, the master regulator of muscle protein synthesis (Przewłócka et al., 2020). When LPS-induced inflammation chronically activates NF-κB, it creates a state where even optimal protein intake fails to robustly stimulate muscle protein synthesis (Aragon et al., 2020; Qi et al., 2022). This means athletes with compromised gut barriers experience diminished returns from their nutritional strategies, effectively "leaving gains on the table" despite consuming adequate protein. To significantly delay or mitigate this anabolic resistance, resistance training is an integral and essential component, as it creates the necessary mechanical stimulus to potentiate the anabolic response, even in older muscle (Aragon et al., 2020). This synergy between regimented physical activity and optimized nutrition is key to maximizing postprandial muscle protein synthesis. To counteract this, research on anabolic resistance provides clear protein intake targets. Studies recommend a daily protein intake of ≥1.6 g/kg of body weight, with optimal per-meal doses of 0.4 g/kg to 0.6 g/kg of protein (Aragon, 2020; Janssen, 2020).

The SCFA Energy Crisis

Compounding this problem, dysbiosis-induced SCFA deficiency creates a secondary energy crisis. Butyrate, propionate, and acetate are not merely metabolic byproducts, they are essential signaling molecules and energy substrates. Butyrate provides approximately 70% of the energy

requirements for colonocytes and drives mitochondrial oxidative phosphorylation through AMP-activated protein kinase (AMPK) activation (Silva, 2020; Kimura, 2013).

When SCFA-producing bacteria decline, intestinal epithelial cells shift from fatty acid oxidation to anaerobic glycolysis, increasing oxygen diffusion into the lumen and promoting facultative anaerobe overgrowth. This metabolic reprogramming reduces epithelial integrity further, creating a vicious cycle where barrier dysfunction impairs SCFA production, and SCFA deficiency exacerbates barrier breakdown (Peng, 2009; Tan, 2014).

Hormonal Signaling Disruption

SCFAs directly influence key anabolic hormones through G-protein coupled receptors GPR41 and GPR43 expressed on enteroendocrine L-cells. Activation of these receptors stimulates glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) secretion, which enhance insulin sensitivity and regulate appetite (Kimura, 2013). Reduced SCFA availability during dysbiosis diminishes this hormonal signaling, impairing the incretin effect and reducing postprandial insulin response.

Furthermore, SCFAs cross the blood-brain barrier and influence central regulation of energy metabolism and satiety (Silva, 2020). Butyrate enhances mitochondrial function in skeletal muscle through PGC-1α activation, improving oxidative capacity and insulin sensitivity. The combination of reduced SCFA production and increased LPS translocation creates a "double hit" that both impairs hormonal signaling and promotes systemic inflammation, synergistically driving anabolic resistance. This dual mechanism—whereby dysbiosis simultaneously increases pro-inflammatory mediators while depriving the host of essential anti-inflammatory metabolites—explains how compromised gut health directly undermines muscle protein synthesis and promotes catabolic signaling, even in the presence of adequate protein intake (Aragon et al., 2022; Przewłócka et al., 2020).

When butyrate-producing bacteria decline, intestinal epithelial cells (IECs) face an energy crisis. Butyrate normally provides approximately 70% of colonocyte energy requirements through mitochondrial β-oxidation (O'Riordan et al., 2022). Reduced SCFA availability forces IEC

mitochondria to shift from oxidative phosphorylation to glycolysis for ATP production (Wang et al., 2021). This metabolic reprogramming has profound consequences for the gut ecosystem.

During glycolysis, IECs consume less oxygen, allowing residual oxygen to diffuse from the vasculature across the epithelium into the intestinal lumen (Byndloss et al., 2017). This oxygenation disrupts the normally anaerobic environment of the colon, which is actively maintained by host mitochondrial metabolism (Byndloss & Bäumler, 2018). The resulting increase in luminal oxygen and nitrate (produced from NO during glycolysis) creates a selective pressure favoring facultative anaerobic and pathogenic Proteobacteria (e.g., *Escherichia coli*, *Salmonella*) while suppressing obligate anaerobic commensals like *Faecalibacterium* and *Roseburia* that specialize in fiber fermentation (Cani, 2018; Lee et al., 2020).

This oxygen-driven dysbiosis initiates a vicious cycle: the expansion of pathogenic bacteria increases luminal LPS and other toxins, further damaging tight junctions and increasing intestinal permeability. LPS translocation then activates TLR4-mediated inflammation, which impairs insulin signaling and mitochondrial function in distant tissues including skeletal muscle (Ji et al., 2025). Concurrently, the loss of butyrate producers eliminates a key energy source for colonocytes, perpetuating the glycolytic shift and continued oxygen leakage. This "oxygen hypothesis" explains how initial SCFA deficiency can trigger progressive dysbiosis through metabolic remodeling of IECs, ultimately compromising systemic metabolic health (Litvak et al., 2018; Yoo et al., 2021).

Solutions: Restoring the Gut-Muscle Axis

The therapeutic potential of targeting the gut-muscle axis is substantial. Dietary interventions that increase fiber intake enhance SCFA production and improve barrier function. The Mediterranean diet, rich in polyphenols and fermentable fibers, has been shown to increase fecal SCFAs, reduce zonulin levels (a marker of permeability), and improve metabolic outcomes (Dmytriv, 2024). Probiotic supplementation with *Lactobacillus* and *Bifidobacterium* species strengthens tight junctions and reduces LPS translocation. In animal models, probiotic administration increased muscle mass and

strength while reducing inflammatory markers (Prokopidis, 2021). Prebiotic fibers like inulin and fructooligosaccharides selectively promote beneficial bacteria, increasing butyrate production and enhancing gut barrier integrity. For athletes specifically, synbiotic approaches combining probiotics with resistance training have shown promise in mitigating exercise-induced gut permeability and preserving muscle mass (Van Krimpen, 2021; Grosicki, 2021). regular moderate exercise itself beneficially modulates the gut microbiota, while excessive high-intensity training without adequate recovery can increase intestinal permeability. This demonstrates the importance of balancing training load with recovery to support a healthy gut environment (Ticinesi, 2019).

Conclusion

The cascade from leaky gut to anabolic resistance represents a critical yet often overlooked factor limiting athletic performance and muscle development. The compromise of intestinal barrier integrity initiates a systemic inflammatory response through LPS translocation that directly impairs insulin signaling and mTOR activation. Concurrent SCFA deficiency starves intestinal epithelial cells of energy, further compromising nutrient absorption and hormonal signaling. This dual mechanism explains why even young, well-nourished athletes can experience anabolic resistance when their microbiome is compromised. The evidence is clear: you're not simply what you eat—you're what your microbiome allows you to absorb. Restoring gut barrier function through targeted dietary interventions, strategic probiotic supplementation, and appropriate exercise prescription represents a frontier in optimizing muscle anabolism and athletic performance. Future research must continue to elucidate the precise mechanisms linking specific microbial populations to anabolic signaling pathways, paving the way for personalized microbiome-based interventions that ensure no gains are left on the table.

Medical and Nutritional Disclaimer

This information is provided for educational purposes only and is not intended to diagnose, treat, cure, or prevent any disease. Individuals must consult a qualified healthcare provider or registered dietitian before making significant changes to their diet or exercise regimen. I**mportant Safety Notice:** Individuals with pre-existing renal impairment, diabetes, or other chronic metabolic conditions should consult a healthcare provider before significantly increasing protein intake

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