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Exploring the Gut-Skin Axis in Psoriasis

Ryan Quigley:
If you treat patients with psoriasis, you already know it's far more than a skin-deep disease. It's a chronic, immune-mediated inflammatory condition with systemic implications — metabolic syndrome, cardiovascular disease, inflammatory bowel disease, even psychiatric comorbidities. But what's increasingly clear is that we may need to think beyond the skin and even beyond the immune system. We may need to think about the gut.

Welcome to *AudioAbstracts* on ReachMD. I'm Ryan Quigley, and today, I'll be talking about a recent comprehensive review in *Frontiers in Microbiology* that explores how gut microbiota are reshaping our understanding of psoriasis pathogenesis and treatment.

So let's start with what's consistently observed. Patients with psoriasis tend to have reduced gut microbial diversity. Measures like the Shannon index and species richness are often lower compared to healthy controls. More specifically, there's typically an increased Firmicutes-to-Bacteroidetes ratio and depletion of beneficial genera such as *Akkermansia* and *Faecalibacterium*, alongside enrichment of potentially pro-inflammatory microbes like *Ruminococcus* and *E. coli*.

Now, why does that matter clinically?

The gut and skin are immunologically linked through what's termed the "gut–skin axis." Under physiologic conditions, gut microbiota help calibrate systemic immune tolerance. So when dysbiosis develops, that balance is disrupted.

Patients with psoriasis have compromised intestinal barrier integrity, also called "leaky gut," with elevated serum markers like Claudin-3 and intestinal fatty acid binding protein, or I-FABP, which indicates increased permeability. This allows lipopolysaccharide and other microbial products to enter systemic circulation, activate dendritic cells and macrophages via Toll-like receptors, and amplify downstream cytokines like IL-17, IL-23, and TNF alpha.

A central mechanism linking these events involves the Treg and Th17 axis — the same immune pathway that's targeted therapeutically in psoriasis.

Th17 development in the gut is microbiota-dependent, with organisms such as *Clostridium*, *Bifidobacterium*, and *Ruminococcus* interacting with epithelial cells and dendritic cells to induce Th17 cell production. But dysbiosis can amplify this. Endoplasmic reticulum stress in intestinal epithelial cells can also initiate purine metabolism pathways that further promote Th17 differentiation, while activated dendritic cells produce IL-23 to stabilize and expand the Th17 lineage.

At the same time, dysbiosis reduces regulatory T-cell populations, disrupting the Treg and Th17 balance and favoring sustained pro-inflammatory cytokine production.

The result is systemic inflammation. Cytokines including IL-17A, IL-22, IL-6, and IFN alpha drive keratinocyte proliferation and inflammatory infiltration in the skin.

In other words, gut barrier dysfunction may be fueling the very inflammatory circuits we target with biologics.

The story becomes even more compelling when we look at microbial metabolites.

Short-chain fatty acids — especially butyrate, acetate, and propionate — are central regulators of immune homeostasis. Butyrate promotes Treg differentiation via HDAC inhibition, suppress pro-inflammatory cytokines, and even support epidermal barrier proteins like filaggrin.

But in psoriasis and psoriatic arthritis, short-chain fatty acid-producing bacteria like *Faecalibacterium* are often reduced, and so the loss of this regulatory metabolite environment may remove an important brake on inflammation.

Tryptophan metabolism is another layer. Gut bacteria metabolize tryptophan into indole derivatives that activate the aryl hydrocarbon receptor, or AhR, a regulator of T-cell differentiation and barrier function. In psoriasis, protective indole metabolites are reduced, while kynurenine pathway metabolites may be elevated, and these alterations correlate with PASI scores. AhR activation can influence both Th17 and Treg polarization, as well as keratinocyte differentiation. And clinically, the efficacy of the AhR agonist tapinarof lends support to this mechanistic pathway.

Bile acids, modified by gut microbes into secondary metabolites such as lithocholic acid derivatives, further modulate Th17 and Treg balance through FXR and TGR5 signaling. Some derivatives inhibit RORγt and suppress Th17 differentiation, while others may exacerbate inflammation depending on context. So the microbiome is a metabolic organ influencing systemic immunity.

So what does this mean therapeutically?

Probiotics — particularly *Lactobacillus* and *Bifidobacterium* strains — have demonstrated reductions in IL-6, IL-17, IL-23, and TNF-alpha expression in both animal models and randomized clinical trials, with associated improvements in PASI scores.

Prebiotics enhance SCFA production and cytokine balance. Some studies have shown prebiotics may improve PASI scores, inflammatory markers, skin thickness, and quality-of-life indices. Synbiotics combine pro and prebiotics and early trials have suggested there is additive benefit.

Fecal microbiota transplantation represents a more aggressive attempt to restore microbial balance. But animal models show that microbiota from healthy donors can mitigate psoriasiform inflammation, whereas microbiota from psoriatic donors can worsen it. Human data remain limited and mixed, with case reports suggesting benefit but randomized data still inconclusive.

Biologic immunosuppressants such as secukinumab and ustekinumab have been shown to alter gut microbial composition, suggesting that immune modulation and microbiota structure influence one another bidirectionally.

So taking all this together, this review highlights that it's important to think of psoriasis as a multisystem inflammatory disorder in which microbial ecology, barrier integrity, and immune regulation are intertwined. Personalized microbiome profiling, metabolite monitoring, and targeted microbial interventions may one day help us reduce relapse, improve durability of response, and address systemic comorbidities.

This has been an *AudioAbstract*, and I'm Ryan Quigley. To access this and other episodes in our series, visit ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!

Reference:

Chen J, Sun K, Zhang X, et al. Psoriasis and gut microbes: research advances from mechanism to therapy. *Front Microbiol*. 2025;16:1711288. doi:10.3389/fmicb.2025.1711288