

# Microbiota-derived UDP-galactose links dietary protein restriction to antitumor immunity in pancreatic cancer

Zong Wei<sup>1,2,\*</sup>

<sup>1</sup>Department of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Scottsdale 85259, USA

<sup>2</sup>Division of Endocrinology, Mayo Clinic Arizona, Scottsdale 85259, USA

\*Correspondence: [wei.zong@mayo.edu](mailto:wei.zong@mayo.edu)

Received: August 24, 2026; Accepted: October 19, 2026; Published Online: October 26, 2026; <https://doi.org/10.59717/j.xinn-nutri.2026.100043>

© 2026 The Author(s). This is an open access article under the CC BY license (<https://creativecommons.org/licenses/by/4.0/>).

Citation: Wei Z. (2026). Microbiota-derived UDP-galactose links dietary protein restriction to antitumor immunity in pancreatic cancer. *The Innovation Nutrition* 1:100043.

Pancreatic ductal adenocarcinoma (PDAC) is characterized by a highly immunosuppressive tumor microenvironment that leads to its limited responsiveness to immune checkpoint blockade. Although adequate or higher protein intake is generally recommended to preserve lean mass and treatment tolerance in patients with cancer, subsets of PDAC display selective amino acid dependencies, and PDAC tumor cells engage in stromal nutrient exchange. Thus, while higher-protein diet could be beneficial in providing nutritional support, low-protein diets may paradoxically target PDAC-specific metabolic and immune vulnerabilities. Dietary interventions have been reported to modify the disease progression through distinct mechanisms, including changing nutrient availability, whole body metabolism, or reshaping the gut microbiota. In a recent study in *Nature Cancer*, Chen and colleagues sought to determine how dietary protein restriction influences PDAC progression and whether the gut microbiota contributes to this response.<sup>1</sup> Their findings revealed a novel link between low-protein diet (LPD)-induced increase in circulating *Blautia coccoides*-derived UDP-galactose and activation of immunostimulatory tumor-associated macrophages (TAMs), which may have significant therapeutic implications (Figure 1).

The authors started by testing whether reduced protein intake alters PDAC progression. In both KPC GEMM and orthotopic models, they found that a 25% reduction, but not 12.5% or 50% reduction, in dietary protein suppressed tumor growth. This non-linear response suggests an interesting nutritional window: 12.5% restriction may be insufficient to remodel the microbiota, whereas 50% restriction could impose host nutritional or immune stress or

disrupt the microbial ecosystem required for benefit. However, LPD did not substantially reduce tumor-cell proliferation, alter circulating lipids, or reduce amino acid availability (although a few circulating amino acids in serum did decrease). Whole tumor RNA-seq did not show changes in cell cycle genes but instead revealed enrichment of immune-activation pathways, suggesting that the antitumor effect could be mediated predominantly through the enhanced antitumor immunity rather than direct nutrient deprivation.

To determine which intratumor immune populations mediate this response, Chen and colleagues first tested LPD in immunodeficient NSG mice, in which the antitumor effect of LPD was lost. scRNA-seq of tumor-infiltrating immune cells identified an increased abundance of macrophages, particularly monocyte-like, inflammatory and interferon-associated TAM states. Depletion of macrophages by anti-CSF and clodronate markedly eliminated the tumor-suppressive effect of LPD, as did depletion of CD8 T cells. These experiments provide solid evidence that immune populations, particularly TAMs, drive the LPD-mediated anti-tumor activity.

The investigators next examined whether changes in the intestinal microbiota were required for LPD-induced immune remodeling. Broad-spectrum antibiotic treatment abolished both tumor suppression and macrophage activation, whereas fecal microbiota transplantation from LPD-treated donors transferred the antitumor phenotype to microbiota-depleted recipients. Metagenomic profiling then identified *B. coccoides* as one of the bacterial species most strongly enriched by LPD. Among several candidate metabolites associated with *B. coccoides*, UDP-galactose was the only metabolite

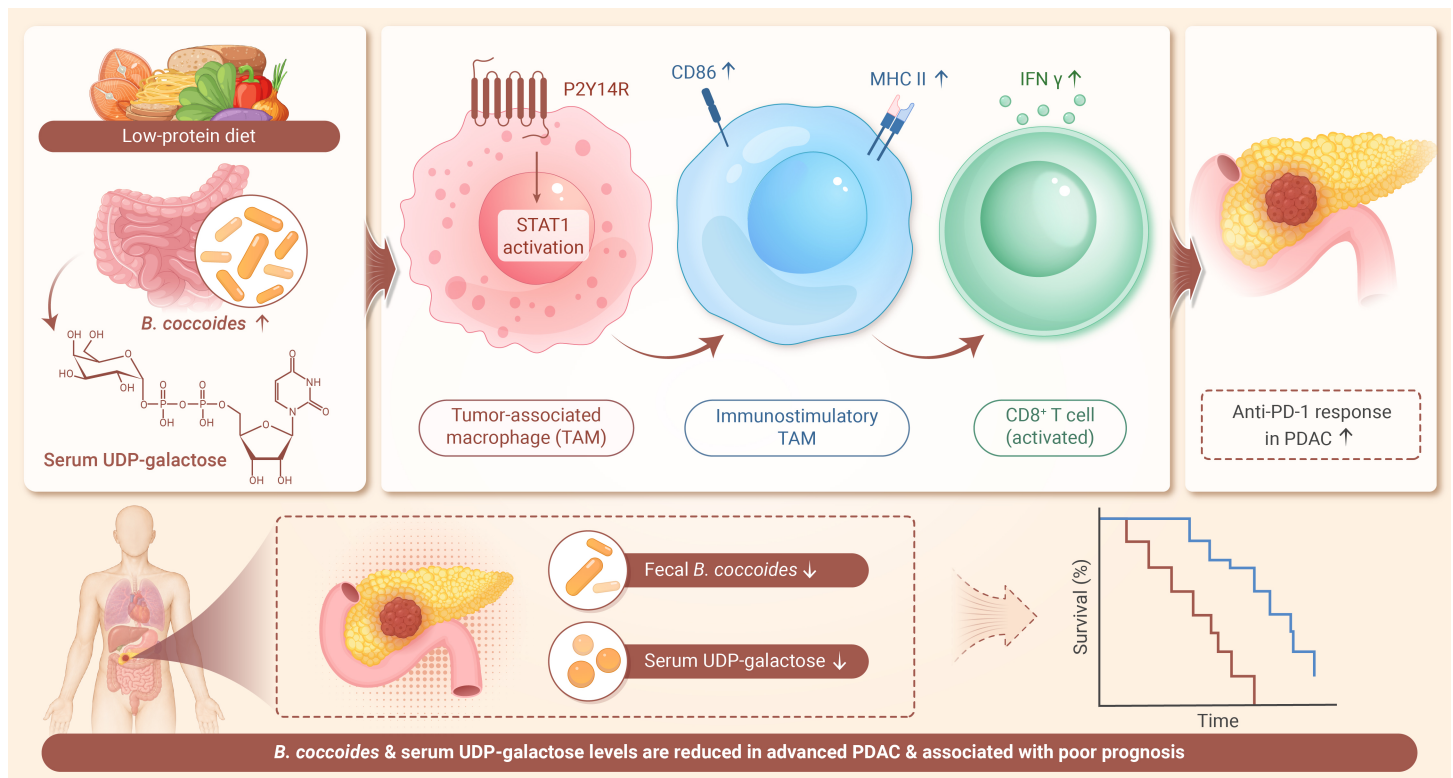


Figure 1. Schematic presentation of the proposed model in the Chen et. al. study.

that consistently promoted an immunostimulatory macrophage phenotype. UDP-galactose did not directly inhibit KPC-cell proliferation, but it reversed tumor-conditioned macrophage immunosuppression and increased their capacity to support CD8 T-cell proliferation and IFN $\gamma$  production. These findings narrowed down the principal biological activity of UDP-galactose to the immune compartment. This stepwise screening and functional validation explains the focus on UDP-galactose rather than the other candidate metabolites.

Although UDP-galactose can be produced in both host tissues and microbiota, the expression of key enzymes for UDP-galactose synthesis did not differ between groups. On the other hand, enzymes required for UDP-galactose biosynthesis were identified in *B. coccoides*, and their abundance increased in fecal microbial communities after LPD treatment. Administration of *B. coccoides* increased circulating UDP-galactose and sufficient to suppress tumor growth, whereas depletion of the gut microbiota reduced intratumoral UDP-galactose in LPD-treated mice. Together, these experiments provide a causal link between LPD, *B. coccoides* abundance, and UDP-galactose in shaping the antitumor immune responses.

The authors then sought to define how extracellular UDP-galactose is sensed by TAMs. Based on the known ligand specificity of the purinergic receptor P2Y14R, they tested whether this receptor mediates the macrophage response to UDP-galactose. Pharmacological inhibition of P2Y14R prevented UDP-galactose-induced macrophage activation. Mechanistically, P2Y14R activation was associated with increased RAR $\beta$  and STAT1 expression and reduced TC45, resulting in enhanced STAT1 phosphorylation.

The therapeutic relevance of this pathway was assessed in the context of immune checkpoint blockade. Anti-PD1 alone had limited activity in the PDAC models, whereas its combination with LPD substantially reduced tumor burden and improved survival. Similar enhancement was observed with either *B. coccoides* or UDP-galactose. The investigators further examined human PDAC samples and found that fecal *B. coccoides* abundance and circulating UDP-galactose concentrations were lower in advanced-stage disease and were associated with more favorable survival. Although these clinical observations are correlative, they provide initial evidence that components of the pathway identified in mice may also be relevant to human PDAC progression. Together, the preclinical data support fecal microbiota transplantation, *B. coccoides* administration, and UDP-galactose supplementation as approaches that recapitulate or enhance the dietary effect. The efficacy and safety of pharmacological P2Y14R agonism remains future investigation.

The study adds to a growing body of evidence that microbiota-derived metabolites influence cancer therapy by acting on distinct cellular components of the tumor microenvironment. In PDAC, microbiome-derived trimethylamine N-oxide has been shown to promote antitumor immunity and improve responsiveness to checkpoint blockade,<sup>2</sup> whereas indole-3-acetic acid can modify the response to chemotherapy through effects on tumor-cell metabolic stress and autophagy.<sup>3</sup> The current study extends these observations by identifying UDP-galactose as a microbial metabolite sensed directly by TAMs. Collectively, these studies revealed diverse mechanisms of microbiota-dependent effects on cancer, which involve changes in microbial composition, the relevant functional metabolites produced by certain species, the effects on intratumor immune cell landscape, and eventually changes of tumor progression or sensitivity to immunotherapies.

An interesting comparison arises from the contrast between extracellular UDP and UDP-galactose signaling in PDAC. Tumor-cell-derived UDP has been reported to signal through P2Y6 on macrophages and support immunosuppressive TAMs associated with resistance to PD1 blockade.<sup>4</sup> In contrast, this study showed that UDP-galactose activates P2Y14R and promotes an immunostimulatory TAM state. These observations illustrate how structurally related extracellular metabolites can generate divergent immunological outcomes through distinct receptors on TAMs. It remains to be determined whether the abundance of these two metabolites is correlated *in vivo* in the context of PDAC.

The findings also broaden the mechanistic interpretation of dietary protein restriction in cancer. Previous work demonstrated that protein restriction can directly alter nutrient competition between tumor cells and TAMs, thereby reprogramming macrophage metabolism and antitumor activity.<sup>5</sup> It's not clear why prolonged LPD does not lead to major amino acid metabolism changes in host tissues in this model. However, the study did provide a novel additional mechanism independent of direct diet effects on tumor growth. In the real world, dietary interventions likely act simultaneously across tumor, immune, host and microbiome and the metabolites it produced, with the relative contribution of each pathway likely determined by tumor type, state, diet composition and probably more importantly, the metabolic state of the host.

Several questions remain to be answered before this can be translated into therapy. The human data do not establish whether reduced *B. coccoides* or UDP-galactose contributes to PDAC progression or instead reflects changes secondary to disease. The human microbiota differs substantially from the murine microbiota, leaving open whether a similar LPD intervention can produce comparable effects in humans. *B. coccoides* is present in the human gut but whether it stably expands after total protein restriction in patients with PDAC is unknown. In addition, sustained protein restriction may be difficult to implement in patients with PDAC due to malnutrition and loss of lean mass. The authors also noted that adherence, nutritional safety and long-term effects on microbiome composition will require careful evaluation in clinical trials.

These considerations may also suggest a more effective strategy of targeting the pathway downstream of the dietary intervention. Manipulation of defined microbial species, microbial biosynthetic pathways, UDP-galactose availability or P2Y14R signaling could potentially reproduce selected immunological effects of LPD without requiring prolonged dietary protein restriction. However, P2Y14R is also expressed in non-macrophage populations such as neutrophils, in which UDP-sugar signaling can promote chemotaxis. Therefore, systemic manipulation of P2Y14R could produce effects outside TAMs, and cell-specific genetic models or targeted delivery will be needed to define its therapeutic window. More broadly, the study provides mechanistic evidence that microbial metabolism can connect dietary exposure to receptor-mediated immune signaling within tumors. Defining comparable metabolite–receptor interactions across cancer types may clarify how variation in diet and microbiome composition contributes to heterogeneity in tumor immunity and treatment response. The same diet-microbiota-metabolite-TAM framework may also be relevant to colorectal, gastric, and hepatocellular carcinomas, although the responsible microbes and metabolites are likely to be tumor specific. In addition, baseline fecal *B. coccoides* abundance and circulating UDP-galactose could be evaluated as biomarkers to stratify patients and monitor responses in precision-nutrition trials.

## REFERENCES

1. Chen Y., Nian F., Wu S., et al. (2026). Low-protein diet enhances antitumor immunity in pancreatic cancer through microbiota-derived UDP-galactose. *Nat. Cancer* Published online August 17, 2026. DOI:10.1038/s43018-026-01222-2.
2. Mirji G., Worth A., Bhat S. A., et al. (2022). The microbiome-derived metabolite TMAO drives immune activation and boosts responses to immune checkpoint blockade in pancreatic cancer. *Sci. Immunol.* **7**:eabn0704. DOI:10.1126/sciimmunol.abn0704
3. Tintelnot J., Xu Y., Lesker T. R., et al. (2023). Microbiota-derived 3-IAA influences chemotherapy efficacy in pancreatic cancer. *Nature* **615**:168–174. DOI:10.1038/s41586-023-05728-y
4. Scolari T., Manco M., Pecqueur M., et al. (2024). Nucleotide metabolism in cancer cells fuels a UDP-driven macrophage cross-talk, promoting immunosuppression and immunotherapy resistance. *Nat. Cancer* **5**:1206–1226. DOI:10.1038/s43018-024-00771-8
5. Zhang X., Li S., Malik I., et al. (2023). Reprogramming tumour-associated macrophages to outcompete cancer cells. *Nature* **619**:616–623. DOI:10.1038/s41586-023-06256-5

## DECLARATION OF INTERESTS

The author declares no competing interests.