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**DIETARY TRYPTOPHAN CATABOLITE RELEASED BY  
INTRATUMORAL *LACTOBACILLUS REUTERI* FACILITATES  
ANTI-PD-L1 THERAPY**

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**Background** The use of probiotic supplementation by cancer patients is increasing, including amongst those undergoing immune checkpoint inhibitor (ICI) therapy. While probiotic supplementation has been identified as an important factor influencing cancer patient responses to ICI therapy in melanoma, the underlying mechanisms of how gut probiotics shape systemic tumor immunity and thereby modulate ICI therapy efficacy remain poorly understood.

**Methods** We used a preclinical melanoma model to identify various probiotic bacteria capable of suppressing tumor growth, and identified the mechanism by which the host-microbial crosstalk enables the most potent tumor-suppressing strain, *Lactobacillus reuteri*, to bolster a strong spontaneous antitumor immunity and increase anti-PD-L1 therapy efficacy. We interrogated the clinical relevance of our findings in a cohort of advanced melanoma patients that either responded or failed to respond to ICI therapy.

**Results** Probiotic bacterium, *L. reuteri*, induces antitumor immunity and promotes ICI therapy in B16 preclinical melanoma via inducing interferon-gamma production by CD8 T cells. *L. reuteri* translocates to, colonizes and persists within melanoma tumors, and this intra-tumoral localization of *L. reuteri* is both necessary and sufficient to mediate antitumor effects in melanoma. *L. reuteri*-mediated tumor suppression occurs in a tumor- and *L. reuteri*-antigen independent fashion. The mechanism by which *L. reuteri* induces this antitumor response is via catabolization of a dietary tryptophan catabolite, indole-3-aldehyde (I3A). I3A is required and sufficient to promote antitumor immunity and facilitate ICI therapy efficacy, and it mediates antitumor immunity via activation of aryl hydrocarbon receptor (AhR) within CD8 T cells. The translational relevancy of I3A's impact on clinical melanoma is supported by our evidence for a role of I3A in promoting anti-PD-1 immunotherapy efficacy and survival in advanced melanoma patients.

**Conclusions** We show that probiotic bacterium *L. reuteri* can translocate to gut-distal melanoma tumors and reveal that its presence within the tumor is required to promote antitumor Tc1 cell immunity and facilitate ICI therapy in preclinical melanoma. Collectively, our findings elucidate a critical microbial-host crosstalk between the microbial released AhR agonist I3A and CD8 T cells within the tumor microenvironment that potently enhances spontaneous antitumor immunity and facilitates ICI therapy efficacy in preclinical melanoma.

**Ethics Approval** Animal care and experimentation were conducted in accordance with NIH guidelines and approved by the Institutional Animal Care and Use Committee at the University of Pittsburgh. Approval to treat patients was obtained from the University of Pittsburgh's Hillman Cancer Center (HCC) Institutional Review Board (No. PRO14030075), and authors attest that signed informed consent was obtained from all patients involved in the study.

**Consent** N/A- no sensitive or identifiable information is included in this study.