Distinct Microbiota Composition in Anorectal Mucosal Melanoma Is Associated with Resistance to Immune Checkpoint Inhibition

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Abstract:

Anorectal mucosal melanoma (AMM) is a rare and aggressive melanoma subtype characterized by poor responses to immune checkpoint inhibitor (ICI) therapy. While cutaneous melanoma metastases to gastrointestinal (GI) sites often retain strong ICI responses, the mechanisms underlying poor responses in AMM remain unclear. Given that AMM arises in microbial rich mucosal environments, we hypothesized that tumor-associated microbiota may contribute to local immune suppression. To investigate this, we performed 16S rRNA gene sequencing on primary AMM tumors and compared their microbial composition with cutaneous melanoma GI metastases (CM-GI-met) and normal mucosal reference samples, including nasal, rectal, and vaginal swabs. AMM tumors were enriched with Firmicutes Clostridia taxa, including Lactospiraceae and Ruminococcaceae, known butyrate producers associated with immunomodulation. In contrast, CM-GI-met tumors exhibited distinct microbial signatures, with a relatively higher abundance of Fusobacteriaceae and Bacteriodaceae. These patients notably had improved ICI responses compared to AMM primaries. These findings are also seen in our orthotopic rectal mouse melanoma model, which showed reduced tumor growth rates, tumor burden, and overall survival in mice treated with combination vancomycin (Gram-positive selective antibiotic which targets Firmicutes Clostridia) and anti-PD-1 therapy compared to controls and monotherapy. Our findings demonstrate that AMM tumors contain a distinct microbiome that may contribute to local tumor evasion whereas CM tumors contain a more ICI-permissive microbiome.