Grain Derived Arabinoxylan Sensitizes Colorectal Cancer to Immune Checkpoint Blockade via Gut Microbial and Metabolic Reprogramming

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Abstract

Background: Dietary fiber plays a critical role in shaping the gut microbiota and regulating antitumor immunity. While fiber intake has been associated with improved responses to immune checkpoint inhibitors (ICIs), current studies have primarily focused on total fiber intake. In contrast, the distinct immunological effects and underlying mechanisms of specific fiber types have received limited attention and remain underexplored. *Methods*: We performed an epidemiological analysis to evaluate the association between total and source-specific fiber intake and colorectal cancer (CRC)–specific mortality, aiming to assess their prognostic relevance. Arabinoxylan, a representative grain-derived fiber, was further evaluated in α-PD-1–resistant CRC mouse models. Immune responses were assessed by flow cytometry, and microbial and metabolic profiles were characterized using metagenomic sequencing and untargeted metabolomics. In vitro coculture assays were conducted to explore interactions between arabinoxylan and Akkermansia muciniphila. *Results*: Only grain-derived fiber intake was significantly associated with reduced CRC-specific mortality. Arabinoxylan synergized with α-PD-1 therapy to suppress tumor growth, enhance $CD8^+$ T cell infiltration and function, and alleviate T cell exhaustion. Multi-omics analyses revealed that the combination remodeled gut microbial composition, enriched A. muciniphila, and upregulated immunoregulatory metabolites including tyrosol, spermidine, and vitamin B6. Coculture assays confirmed that arabinoxylan promotes A. muciniphila growth by stimulating vitamin B6 biosynthesis in commensal bacteria, identifying VB6 as a key microbial metabolite mediating this interaction. *Conclusion*: Arabinoxylan enhances α-PD-1 efficacy by boosting $CD8^+$ T cell responses and remodeling the gut microbiota–metabolite axis. These findings support arabinoxylan as a promising dietary intervention to overcome immunotherapy resistance and improve CRC treatment outcomes.

Keywords

Arabinoxylan, Dietary Fiber, Colorectal Cancer, Immune Checkpoint Blockade, Gut Microbiota, *Akkermansia Muciniphila*