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Letter to the Editor

The dichotomous role of *A. muciniphila* in CRC: from probiotic to postbiotic

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To the Editor,

We recently engaged with the systematic review by Soheilipour *et al.*[1], concludes that *Akkermansia muciniphila* primarily acts as a pathobiont in colorectal cancer (CRC) by exacerbating tumor progression. While the authors provide a comprehensive analysis of the bacterium's pathobiont potential (particularly its propensity to exacerbate colitis-associated tumorigenesis by degrading mucins in inflamed environments) we wish to underscore a pivotal therapeutic evolution: the transition from live probiotics to targeted postbiotics (defined as non-viable bacterial products or metabolic byproducts that confer a health benefit to the host).

Emerging evidence indicates that the functional role of *A. muciniphila* is highly context-dependent [2]. In "susceptible clinical settings," such as inflamed environments or post-antibiotic contexts where the microbiome is depleted, live *A. muciniphila* may lead to excessive mucin degradation [1]. This erosion of the mucus layer can compromise intestinal barrier integrity, allowing for increased translocation of pro-inflammatory factors and promoting inflammation-driven tumorigenesis. Consequently, for CRC patients (who often present with pre-existing dysbiosis and epithelial dysfunction) the administration of live strains carries a significant risk-to-benefit ratio [1,2].

In contrast, individual molecular components of *A. muciniphila* reliably exhibit anti-tumorigenic properties without the risk of barrier disruption [2]. For instance, the outer membrane protein Amuc_1100 has been demonstrated to attenuate tumorigenesis by activating cytotoxic T lymphocytes (CTLs) [3]. Furthermore, the recently characterized acetyltransferase Amuc_2172, delivered via extracellular vesicles, has been shown to epigenetically reprogram the tumor microenvironment, thereby enhancing the efficacy of PD-1 blockade [4].

These findings suggest that the future role of *A. muciniphila* in oncology should pivot away from effective colonization and instead focus on the precision application of its bioactive molecules. We advocate for future clinical trials to prioritize these postbiotic derivatives (Amuc_1100, Amuc_2172, and extracellular vesicles) in order to exploit the immunological benefits of the bacterium while mitigating its pathobiont liabilities.

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