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Protective Effect of Weissella paramesenteroides WpK4 on Murine Intestinal Mucositis: The Role of Tryptophan Metabolism

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The intestinal microbiota plays a crucial role in host homeostasis, with the balance between its components defining eubiosis, a state associated with host health. Dysbiosis, on the other hand, results from the loss of this balance and may be implicated in the development of various pathological conditions. Intestinal mucositis induced by chemotherapeutic agents, such as 5-fluorouracil (5-FU), is an example of an inflammatory condition in which dysbiosis can serve as an important biomarker. In this context, probiotics have been investigated as a therapeutic approach to restore eubiosis and mitigate the adverse effects of dysbiosis. Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits to the host, and evidence suggests they may be effective in controlling dysbiosis associated with inflammatory conditions. The bacterial strain *Weissella paramesenteroides* WpK4, isolated from the nasopharynx of weaned pigs, has shown probiotic potential, exhibiting beneficial effects in experimental models of infection and inflammation. A distinctive feature of this strain is the presence of the tryptophan operon in its genome, enabling it to synthesize tryptophan (TRP), an essential amino acid involved in critical biological processes, such as modulation of inflammatory responses and cellular signaling. Therefore, this study aimed to investigate the impact of tryptophan metabolism on the protection conferred by *W. paramesenteroides* WpK4 in a murine model of 5-FU-induced intestinal mucositis. Metabolic profiling of *W. paramesenteroides* WpK4 revealed the production of TRP, tryptamine (TAM), indole-3-acetic acid (IAA), and indole aldehyde (IAld), compounds known for their bioactive properties related to tryptophan metabolism. In the 5-FU-induced mucositis model, oral administration of *W. paramesenteroides* WpK4 resulted in 100% survival of the animals, while the control group, treated with 0.9% saline solution, showed a survival rate of 60%. Moreover, animals treated with *W. paramesenteroides* WpK4 exhibited lower morbidity and preservation of the intestinal microbiota composition, characteristics suggesting favorable modulation of the inflammatory response. Molecular analysis also indicated an increase in the expression of genes related to tryptophan metabolism in the host, suggesting the activation of the AhR (aryl hydrocarbon receptor) pathway, which may be involved in the observed protection. These results indicate that *W. paramesenteroides* WpK4 could represent a promising therapeutic strategy for the treatment of chemotherapeutic-induced intestinal mucositis, with its tryptophan metabolism possibly mediating the observed protective effects. The modulation of the intestinal microbiota and activation of tryptophan signaling pathways are mechanisms that warrant further investigation for the development of probiotic-based therapies in inflammatory contexts.

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