ENGINEERING HUMAN MICROBIOTA FOR DISEASE PREVENTION AND THERAPY

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Introduction: Bacteria living with us in commensalism at mucosal districts constitute a whole living kingdom, namely the human microbiota. Commensal bacteria have several beneficial effects and several strains have been identified to possess direct proactive interaction with the human immune system and metabolism, and more complex effects on behavior and the central nervous system. The overall protective effect exerted by the microbiota could therefore be potentiated by genetically engineering specific bacterial species for the delivery of prophylactic or therapeutic recombinant proteins. Among the diverse applications of this strategy, the engineering of anti-HIV live microbicides based on the genetic modification of lactic acid bacteria to express recombinant HIV protein blockers has been extensively investigated. Reported in detail here is the production of lactobacilli secreting recombinant human CCL5 variants acting as extremely potent HIV entry inhibitors.

Methods: Following rational design of CCL5 mutants, recombinant lactobacilli were generated to secrete CCL5 mutants that, after semi-purification from supernatant, were tested for anti-HIV activity. Successful mutations were integrated in CCL5 via iterative cycles of engineering, semi-purification and activity testing, leading to the production of the most potent HIV inhibitors to date.

Results: The dual use of engineered lactobacilli (as CCL5 mutants screening platform and as lead microbicides) led to the selection and initial development of potent anti-HIV live microbicides based on the expression and secretion of CCL5 variants with potentiated CCR5 binding affinity. Aside HIV, these CCL5 variants (either as lactobacilli-secreted live therapeutics or as purified proteins) could be used against a wealth of inflammation-related pathologies where the CCL5:CCR5 axis is of major relevance, including cancer, atherosclerosis and inflammatory bowel disease.

Conclusion: The successful generation of potent CCR5 antagonists based on CCL5 engineering via the use of recombinant commensal bacteria constitutes a paradigmatic example of how microbiota engineering could enhance human health protection.