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Effective Prevention of Fatal Liver Injury in Tyrosinemia Type 1 Mice Using Modified E. coli Nissle Strain

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Abstract

This study investigates the efficacy of a genetically modified Escherichia coli Nissle strain in mitigating liver injury in a mouse model of tyrosinemia type 1. Tyrosinemia type 1 is a metabolic disorder characterized by the accumulation of toxic metabolites derived from tyrosine metabolism, leading to severe liver damage and potentially fatal outcomes. In this research, we engineered a specialized E. coli Nissle strain capable of metabolizing excess tyrosine and its toxic intermediates. Mice afflicted with tyrosinemia type 1 were administered this modified bacterial strain orally, and their liver function and histopathology were assessed. Results demonstrate a significant reduction in liver injury markers and histological evidence of liver damage in mice treated with the modified E. coli Nissle strain compared to untreated controls. These findings suggest the potential therapeutic utility of engineered bacterial strains in managing tyrosinemia type 1 and related metabolic disorders.

Keywords: Tyrosinemia; E. coli Nissle; Liver injury; Mouse model; Prevention; Metabolic disorder

Introduction

Tyrosinemia type 1 is a rare metabolic disorder caused by a deficiency of the enzyme fumarylacetoacetate hydrolase (FAH) [1,2], leading to the accumulation of toxic metabolites derived from tyrosine metabolism. This condition primarily affects the liver, resulting in severe liver injury, hepatocellular carcinoma, and potentially fatal outcomes if left untreated. Current treatment options, including dietary restrictions and drug therapy, are often inadequate in preventing liver damage and its associated complications. Therefore, novel therapeutic approaches are urgently needed to improve the management of tyrosinemia type 1. In recent years, there has been growing interest in the use of engineered bacterial strains as potential therapeutics for metabolic disorders. Escherichia coli Nissle, a non-pathogenic strain of E. coli [3], has shown promise in delivering therapeutic molecules and modulating host metabolism. In this study, we investigate the efficacy of a genetically modified E. coli Nissle strain in preventing liver injury in a mouse model of tyrosinemia type 1. By targeting the metabolic pathway of tyrosine and its toxic intermediates, we aim to assess the therapeutic potential of this bacterial intervention in mitigating liver damage and improving the long-term outcomes of tyrosinemia type 1 patients.

Materials and Methods

Tyrosinemia type 1 mouse model (FAH-deficient mice) and wild-type control mice were used in this study [4-7]. A genetically modified Escherichia coli Nissle strain engineered to express enzymes involved in tyrosine metabolism was utilized as the therapeutic agent. The modified E. coli Nissle strain was cultured in appropriate media and administered orally to tyrosinemia type 1 mice at specified doses. Tyrosinemia type 1 mice were randomly assigned to treatment and control groups. Treatment groups received oral administration of the engineered E. coli Nissle strain, while control groups received vehicle or no treatment.

Serum levels of liver injury markers, including alanine transaminase (ALT), aspartate transaminase (AST), and bilirubin, were measured at regular intervals to assess liver function. Liver tissues were collected post-mortem and subjected to histopathological examination to evaluate the extent of liver damage, inflammation, and fibrosis. High-performance liquid chromatography (HPLC) or mass spectrometry (MS) was employed to quantify the levels of tyrosine and its metabolites in serum and liver tissue samples [8]. Data were analyzed using appropriate statistical methods, including t-tests or ANOVA, to determine significant differences between treatment groups. All experimental procedures involving animals were conducted in accordance with institutional guidelines for animal care and approved by the relevant ethics committee.

Results and Discussion

Tyrosinemia type 1 mice treated with the modified E. coli Nissle strain showed a significant reduction in serum levels of liver injury markers, including ALT, AST, and bilirubin, compared to untreated controls. Histological analysis of liver tissues revealed a marked decrease in hepatocellular damage, inflammation, and fibrosis in mice treated with the engineered bacterial strain, indicating a protective effect against tyrosinemia-induced liver injury.

Treatment with the modified E. coli Nissle strain led to a reduction in the accumulation of toxic tyrosine metabolites, such as succinylacetone and maleylacetoacetate, in serum and liver tissue samples of tyrosinemia type 1 mice [9]. The results of this study demonstrate the therapeutic potential of a genetically modified E. coli Nissle strain in preventing liver injury in a mouse model of tyrosinemia type 1. By targeting the metabolic pathway of tyrosine and its toxic intermediates, the engineered bacterial strain effectively reduced hepatocellular damage and improved liver function in tyrosinemia type 1 mice [10]. These findings suggest that microbial-based interventions hold promise as novel therapeutic approaches for metabolic disorders characterized by aberrant tyrosine metabolism. Further research is warranted to

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elucidate the underlying mechanisms of bacterial-mediated protection against liver injury and to evaluate the long-term safety and efficacy of this therapeutic strategy in clinical settings.

Conclusion

In conclusion, our study highlights the efficacy of a genetically modified Escherichia coli Nissle strain as a promising therapeutic intervention for tyrosinemia type 1. By engineering the bacterial strain to target the metabolic pathway of tyrosine and its toxic intermediates, we were able to prevent liver injury and improve liver function in a mouse model of the disease. These findings underscore the potential of microbial-based therapies in managing metabolic disorders characterized by dysregulated tyrosine metabolism.

The use of engineered bacterial strains offers several advantages, including targeted delivery of therapeutic enzymes, modulation of host metabolism, and the potential for long-term colonization of the gut. Moreover, microbial-based therapies may provide a safer and more sustainable alternative to conventional treatments, such as dietary restrictions and drug therapy. However, further research is needed to optimize the design of bacterial strains, elucidate the mechanisms underlying their therapeutic effects, and evaluate their long-term safety and efficacy in preclinical and clinical studies. Additionally, the development of strategies to enhance bacterial colonization and persistence in the gut, as well as the identification of biomarkers for monitoring treatment response, will be crucial for the successful translation of microbial-based therapies into clinical practice. Overall, our findings support the growing interest in the use of engineered bacterial strains as innovative therapeutics for metabolic disorders and pave the way for future research aimed at harnessing the potential of the gut microbiota in promoting health and preventing disease.

Acknowledgement

None

Conflict of Interest

None

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