Enzyme Biotechnology

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Executive Editor

Can Gut Enzyme Fight Deadly Drug-Resistant Infections?

The resurgence of microbial infections caused by multidrug-resistance (MDR) strains poses a serious healthcare challenge for public. According to some survey and estimates for the public healthcare risks for the coming decades, millions of people around the world are considered at risk of serious bacterial infections due to the emergence of MDR [1, 2]. To mitigate this serious threat to the global human healthcare, biotechnologists and medical researchers are working together to discover novel antimicrobial molecules and viable natural pathways to combat this challenge. To this end, the human gut microbiome is being further researched that has largely remained unexplored so far. It has been suggested that the human gut microbiome could potentially contain a treasure trove of information about new natural molecules including ribosomally-synthesized and post-translationally modified peptides (RiPPs) that could be leveraged for the development of powerful probiotic and drugs [3]. Previous researches have shown that RiPPs can be biosynthesized from a genetically encoded precursor peptide that usually contains an N-terminal leader sequence and a C-terminal core peptide [4]. Further, researchers showed a subclass of bacteriocins among these peptides, which is known as sactipeptides [3, 5, 6]. This important subclass of peptides is believed to hold the key to exploit human gut microbiome for potential development of natural antibiotic that can fight drug-resistant infections. However, the important biological activity of the sactipeptide subclass of RiPPs is not yet fully revealed and characterized [3].

Antimicrobial Molecule Produced by the Human Microbiota Gut Offers Promise to Fight Drug-Resistant Infections

Researchers for the first time reported the *in-vivo* and *in-vitro* production of the Ruminococcin C1 (Rum C1) sactipeptide and its functional and conformational characterizations. In a research of major significance, the strong antimicrobial activity against Gram-positive pathogens including MDR strains and the lack of toxic effect toward eukaryotic cells were demonstrated.

Rum C1 was shown to be promising for the development of natural antibiotic produced by a human gut symbiont. Additionally, its producer strain *Ruminococcus gnavus E1* could potentially be used as a powerful natural probiotic for gut health enhancement, Figure 1 [3].

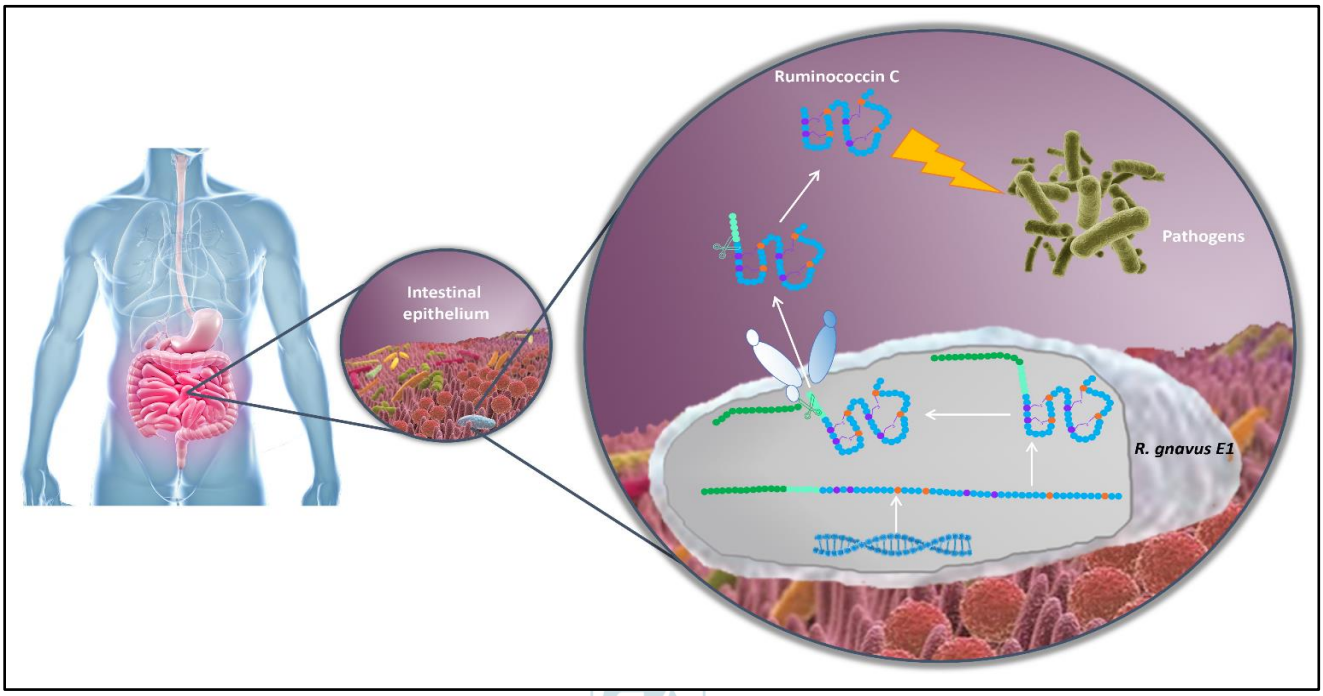

*Figure 1: A schematic illustration of the production of antimicrobial and safe sactipeptide Rum C1 from the human symbiont R. gnavus E1. It is externally activated in the gut by the host digestive system [**Source:** Science Advances 2019].*

In a significant breakthrough, researchers found broad-spectrum antimicrobial activity of RumC1 compound that was isolated from a gut bacterium of the Firmicutes group. It exhibited antimicrobial properties when employed even against antibiotic-resistant Clostridia and Staphylococci. Rum C1 that was ribosomally synthesized and post translationally modified did not show any toxicity unlike other conventional antibiotics. Most importantly, it did not show any signs of triggering towards development of drug resistance. This implies that Rum C1 could even be employed to work in tandem with other antimicrobial agents to enable minimizing bacterial resistance and to fight clinical pathogens [3].

The method employed by the researchers involved purifying Rum C1 from rat feces. This resulted in the production of an active, mature molecule identical to the peptides that naturally reside in human intestines. The antimicrobial activity was subsequently tested against a broad range of bacteria, including pathogens and strains resistant to multiple antibiotic drugs. They then performed safety assays to test its effect on human cell lines and observed that the peptide isolated from *R. gnavus* E1 fights Gram-positive bacteria quite effectively [3].

The Potential of Rum C1 for Use against Food Borne Pathogens and MDR Bacteria

The broad antimicrobial spectrum of Rum C1 was investigated on a vast array of Gram-positive and Gram-negative bacteria, including pathogens and MDR strains. Rum C1 was shown to be safe for use against pathogens and MDR bacteria. Further, researchers demonstrated the of Rum C1 against a range of pathogenic Clostridium species, which is known as the third cause of foodborne infections in the United States after Norovirus and Salmonella spp. according to the Centers for Disease Control and Prevention (CDC). Rum C1 was also observed to be active against a range of Gram-positive organisms such as *Staphylococcus aureus* and MDR strains including vancomycin-resistant *Enterococcus faecalis*, nisin-resistant *Bacillus subtilis* or methicillin-resistant *S. aureus* (MRSA) [3].

The demonstrated high potency of Rum C1 against pathogenic strains coupled with its unique functionalities of safety features that include unaffected eukaryotic cells by the applications of Rum C1 makes it a significantly promising approach to fight MDR. Further, the absence of resistance development makes Rum C1 a promising candidate either as therapeutic agent or as food safety agent. Based on these findings, it can be further envisioned that Rum C1 sactibiotics and other groups of bacteriocins could be employed in combinatorial therapies in future with other antimicrobial agents that could include antibiotics [3].

Concluding Remarks

The biotech R&D advances that are being made in developing and optimizing a bio-based process to purify a natural molecule exhibiting antibiotic activity produced by a human intestinal symbiont offer tremendous promise in combating MDR in future. We anticipate that this paves the way for the development of new therapeutic strategies for human or animal health. These include drug optimization and other processes in combination with antimicrobial agents or antibiotics.

References

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