【Grant-in-Aid for Scientific Research (S)】

Understanding a mechanism of an onset of colorectal cancer by colibactin and finding compounds inhibiting colibactin biosynthetic enzymes

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Project Information	Project Number : 22H04979　　Project Period (FY) : 2022-2026 Keywords : colibactin, natural product, genotoxicity, biosynthesis, colorectal cancer

Purpose and Background of the Research

●Outline of the Research

This study aims to understand the mechanism of onset of colorectal cancer associated with the human microbiota. The findings from this study will be applied to the development of cancer prevention measures. Approximately 70% of colon cancer patients carries Escherichia coli that produces a genotoxic compound called colibactin. Based on the proposed chemical structure and mouse model studies of colibactin, *E. coli* is suggested to be implicated in colorectal carcinogenesis through the production of colibactin. In contrast, colibactin-producing *E. coli* has also been used as a probiotic to treat inflammatory bowel disease in Europe without increasing cancer risk. Thus, colibactin-producing strains are not treated as a risk factor or recognized as a molecular marker for colorectal cancer currently.

Here, we hypothesize that only a subset of colibactin-producing *E. coli*, namely high colibactin producers, induces colorectal cancer. This hypothesis is based on the experimental findings that the *E. coli* isolate *E. coli*-50 from a colorectal cancer tissue exhibits extremely high colibactin production, and the *E. coli*-50 genome carries genes that code for unique pathogenic toxins. In this study, we will evaluate the validity of our hypothesis and identify *E. coli* characteristics responsible for colorectal carcinogenesis.

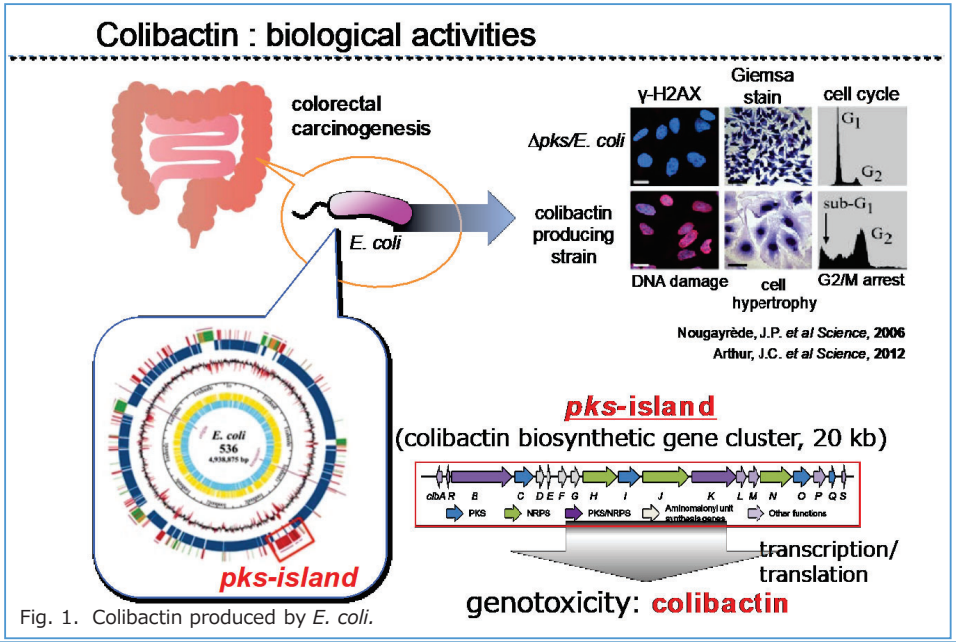

Fig. 1. Colibactin produced by *E. coli*.

●Chemical structure of colibactin

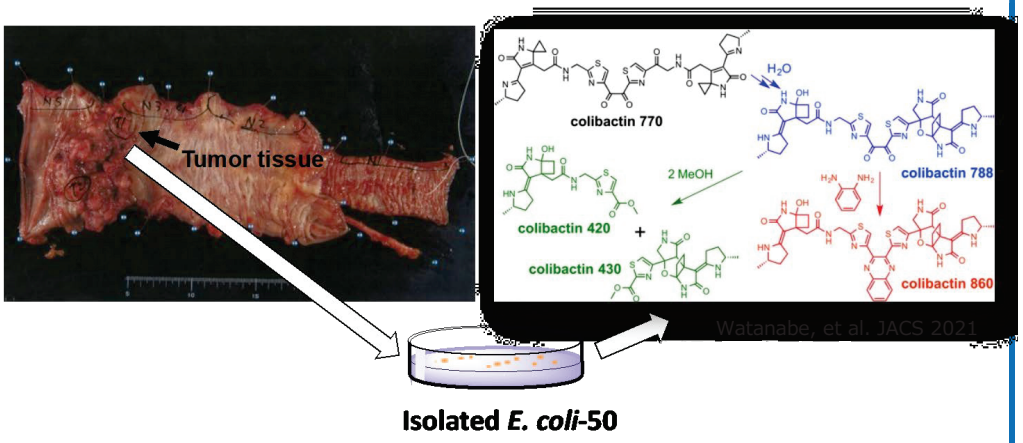

Fig. 2. Chemical structure of colibactin.

Expected Research Achievements

●Detection of colibactin producing strain

The aim of this study is to design a fluorescence probe that is activated specifically by an enzymatic activity associated with Clb biosynthesis. Use of such a probe would allow characterization of the Clb biosynthetic activity in each of the large number of *E. coli* isolates that can be collected from an individual in a high-throughput fashion without requiring highly specialized analytical instruments（Figure 3）.

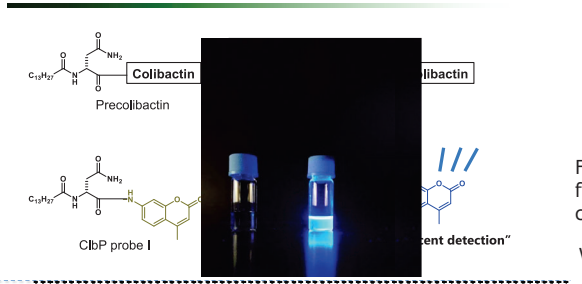

Fig. 3. Establishment of fluorescence probe for detecting colibactin producing strain.

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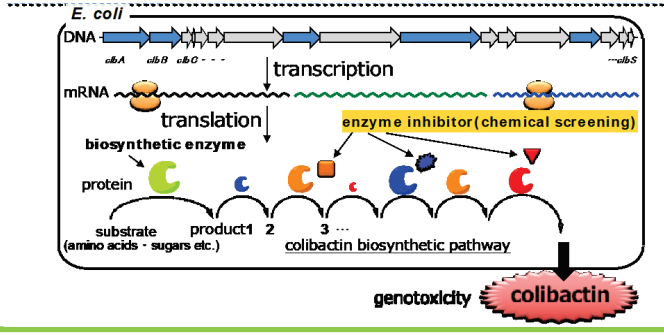

Fig. 4. Development of inhibitor for colibactin biosynthetic pathway.

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