# 腸内細菌叢と腸管感染症

金　倫基
慶応義塾大学薬学部創薬研究センター

**略歴**

1977年東京都生まれ。2000年 北里大学薬学部卒業。2005年 北里大学大学院薬学学研究科博士課程（微生物学専攻）修了。2006年 University of Michigan Medical School (USA) Post-doctoral Fellow。2011年 筑波大学医学医療系助教（免疫学）。2013年 University of Michigan Medical School (USA) Research Investigator。2015年 Vedanta Biosciences, Inc. (USA) Senior Scientist。2016年 慶應義塾大学薬学部生化学講座専任准教授。2018年 慶應義塾大学薬学部創薬研究センター教授。

主な研究テーマ

腸内細菌が炎症性・代謝性疾患に与える影響の解明。マイクロバイオームモジュレーターに関する研究。

主な受賞

2010年：腸内細菌学会研究奨励賞、2013年：CCFA career development award

## 要約

正常な腸内細菌叢は細菌間で安定なコミュニティーを形成しており、外来の病原性細菌の侵入に対して強い抵抗性を示すことが知られている。腸内細菌による病原性細菌の侵入・定着の阻害作用は、コロナイゼーションレジスタンス（Colonization resistance; CR）と呼ばれている。抗菌薬の投与などにより、腸内細菌叢によるCRが低下すると、腸管病原性大腸菌（EPEC: Enteropathogenic *Escherichia coli*）や*Salmonella* などの病原細菌（Pathogens）や、*Clostridioides difficile* などの病原性常在細菌（Pathobionts）の定着や増殖を許してしまう。

腸管感染症を治療する目的で、腸内細菌叢によるCRを臨床応用する動きがこの十数年の間に出てきている。2013年にNEJM誌で、再発性*C. difficile* 感染症（rCDI：recurrent *C. difficile* infection）に便微生物移植法（FMT: Fecal Microbiota transplantation）が著効することが報告されて以来[1]、rCDIに対するFMT用糞便サンプルの医薬品としての開発が進められた。そして2022年には、オーストラリアとアメリカで、rCDIに対するFMT用の糞便サンプルが医薬品として承認されている[2,3]。

我々は、腸内細菌叢の主要構成メンバーである*Clostridium* cluster IV & XIVaに属する腸内細菌が、腸管病原細菌に対して強いCRを示すことを明らかにした[4]。この知見に合致して、ヒトの糞便をエタノール処理したFirmicutes門菌（主に*Clostridium* cluster IV & XIVa菌）の芽胞から構成されるrCDIに対する経口治療薬が2023年4月にアメリカで承認された[5]。さらに、*Clostridium* cluster IV & XIVaに属する8種類の腸内細菌コンソーシアム（VE303）がCDIマウスの生存率を大きく上昇させることを発見し[6]、2022

年にはrCDI患者に対するフェーズII試験でVE303の有効性が確認された[7]。

現在は、CRに影響を与える食事因子および腸内細菌代謝物の同定と作用メカニズムの解明に取り組んでいる。我々は、食餌由来のタンパク質源が特定の腸内細菌を介してマウスのCDI病態を変化させることや[8]、D－アミノ酸の一つであるD－トリプトファンが腸内のpathogenやpathobiontの菌体内の代謝を変化させることにより、増殖を抑制し、腸炎を抑制することを見出した[9]。

そこで本講演ではCRに関するこれまでの知見についてお話したい。

参考文献


1 van Nood, E. *et al*. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* **368**, 407-415, doi:10.1056/NEJMoa1205037 (2013).

2 Khanna, S. *et al*. Efficacy and Safety of RBX2660 in PUNCH CD3, a Phase III, Randomized, Double-Blind, Placebo-Controlled Trial with a Bayesian Primary Analysis for the Prevention of Recurrent *Clostridioides difficile* Infection. *Drugs* **82**, 1527-1538, doi:10.1007/s40265-022-01797-x (2022).

3 Tucker, E. C. *et al*. Stool donor screening within a Therapeutic Goods Administration compliant donor screening program for fecal microbiota transplantation. *JGH Open* **7**, 172-177, doi:10.1002/jgh3.12874 (2023).

4 Kim, Y. G. *et al*. Neonatal acquisition of Clostridia species protects against colonization by bacterial pathogens. *Science* **356**, 315-319, doi:10.1126/science.aag2029 (2017).

5 Feuerstadt, P. *et al*. SER-109, an Oral Microbiome Therapy for Recurrent *Clostridioides difficile* Infection. *N Engl J Med* **386**, 220-229, doi:10.1056/NEJMoa2106516 (2022).

6 Dsouza, M. *et al*. Colonization of the live biotherapeutic product VE303 and modulation of the microbiota and metabolites in healthy volunteers. *Cell Host Microbe* **30**, 583-598 e588, doi:10.1016/j.chom.2022.03.016 (2022).

7 Louie, T. *et al*. VE303, a Defined Bacterial Consortium, for Prevention of Recurrent *Clostridioides difficile* Infection: A Randomized Clinical Trial. *JAMA* **329**, 1356-1366, doi:10.1001/jama.2023.4314 (2023).

8 Yakabe, K. *et al*. Dietary-protein sources modulate host susceptibility to *Clostridioides difficile* infection through the gut microbiota. *Cell Rep* **40**, 111332, doi:10.1016/j.celrep.2022.111332 (2022).

9 Seki, N. *et al*. (D)-Tryptophan suppresses enteric pathogen and pathobionts and prevents colitis by modulating microbial tryptophan metabolism. *iScience* **25**, 104838, doi:10.1016/j.isci.2022.104838 (2022).

# Gut microbiota and enteric infection

Yun-Gi Kim
Research Center for Drug Discovery, Faculty of Pharmacy, Keio University, Tokyo

## Brief curriculum vitae

Born in Tokyo (Japan) in 1977. Graduated from School of Pharmaceutical Sciences, Kitasato University in 2000, and completed doctoral course in Microbiology, Graduate School of Pharmaceutical Sciences, Kitasato University in 2005. Post-doctoral fellowship at the University of Michigan Medical School (USA) in 2006, Assistant Professor at Faculty of Medicine, the University of Tsukuba in 2011, Research Investigator at the University of Michigan Medical School (USA) in 2013, Senior Scientist at Vedanta Biosciences, Inc. (USA) in 2015. Associate Professor at Faculty of Pharmacy, Keio University in 2016 and Professor at Research Center for Drug Discovery, Faculty of Pharmacy, Keio University in 2018.

Main research interests: Role of gut microbiota on inflammatory and metabolic diseases. Gut microbiome modulators.

Awards: 2010; The Intestinal Microbiology Society Incentive Award, 2013: CCFA career development award.

## Abstract

Normal gut microbiota forms stable communities among bacteria and exhibits strong resistance to the invasion of foreign pathogenic bacteria. This inhibitory effect of gut microbiota on the invasion and colonization of pathogenic bacteria is called colonization resistance (CR). When CR by the gut microbiota is suppressed due to the treatment with antibiotics, etc., pathogens such as Enteropathogenic *Escherichia coli* (EPEC) and *Salmonella*, and pathobionts such as *Clostridioides difficile* colonize and proliferate in the intestine.

In the last ten years, there have been moves to the clinical application of CR by the gut microbiota for the purpose of treating enteric infections. Since the report published at NEJM in 2013 has shown that fecal microbiota transplantation (FMT) is effective in recurrent *C. difficile* infection (rCDI)[1] , the development of stool samples as medicine has proceeded. And in 2022, fecal samples for FMT for rCDI have been approved as medicines in Australia and the United States[2,3].

We have shown that gut bacteria belonging to *Clostridium* cluster IV & XIVa, which are major members of the gut microbiota, exhibit strong CR against enteropathogenic bacteria[4]. Consistent with this finding, an oral medicine with ethanol-treated human fecal samples composed of spores of Firmicutes (mainly Clostridium cluster IV & XIVa) for rCDI was approved in the United States in April 2023[5]. In addition, we discovered bacterial consortium consisting of 8 strains

of human gut bacteria belonging to *Clostridium* cluster IV & XIVa (VE303) significantly improved the survival of CDI mice[6]. In 2022, a phase II study in patients with rCDI confirmed the efficacy of VE303[7].

We are currently focusing on identifying dietary factors and gut bacterial metabolites that affect CR and their mechanism of action. We have found that dietary protein sources influence the pathogenesis of CDI in mice through specific gut bacteria[8]. Besides, D-tryptophan inhibited the proliferation of gut pathogens and pathobionts by altering their metabolism, thereby suppressing intestinal inflammation[9].

In this symposium, I would like to discuss current our knowledge regarding CR.

References


1 van Nood, E. *et al*. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* **368**, 407-415, doi:10.1056/NEJMoa1205037 (2013).

2 Khanna, S. *et al*. Efficacy and Safety of RBX2660 in PUNCH CD3, a Phase III, Randomized, Double-Blind, Placebo-Controlled Trial with a Bayesian Primary Analysis for the Prevention of Recurrent *Clostridioides difficile* Infection. *Drugs* **82**, 1527-1538, doi:10.1007/s40265-022-01797-x (2022).

3 Tucker, E. C. *et al*. Stool donor screening within a Therapeutic Goods Administration compliant donor screening program for fecal microbiota transplantation. *JGH Open* **7**, 172-177, doi:10.1002/jgh3.12874 (2023).

4 Kim, Y. G. *et al*. Neonatal acquisition of Clostridia species protects against colonization by bacterial pathogens. *Science* **356**, 315-319, doi:10.1126/science.aag2029 (2017).

5 Feuerstadt, P. *et al*. SER-109, an Oral Microbiome Therapy for Recurrent *Clostridioides difficile* Infection. *N Engl J Med* **386**, 220-229, doi:10.1056/NEJMoa2106516 (2022).

6 Dsouza, M. *et al*. Colonization of the live biotherapeutic product VE303 and modulation of the microbiota and metabolites in healthy volunteers. *Cell Host Microbe* **30**, 583-598 e588, doi:10.1016/j.chom.2022.03.016 (2022).

7 Louie, T. *et al*. VE303, a Defined Bacterial Consortium, for Prevention of Recurrent *Clostridioides difficile* Infection: A Randomized Clinical Trial. *JAMA* **329**, 1356-1366, doi:10.1001/jama.2023.4314 (2023).

8 Yakabe, K. *et al*. Dietary-protein sources modulate host susceptibility to *Clostridioides difficile* infection through the gut microbiota. *Cell Rep* **40**, 111332, doi:10.1016/j.celrep.2022.111332 (2022).

9 Seki, N. *et al*. (D)-Tryptophan suppresses enteric pathogen and pathobionts and prevents colitis by modulating microbial tryptophan metabolism. *iScience* **25**, 104838, doi:10.1016/j.isci.2022.104838 (2022).