腸内細菌叢と発がん：メカニズムとそのきっかけ

Ryan Balfour Sartor
ノースカロライナ大学チャペルヒル校　微生物学・免疫学 米国

略歴：

米国ルイジアナ州シュリーブポート生まれ。ワシントン＆リー大学（バージニア州レキシントン）、ベイラー医科大学（テキサス州ヒューストン）を卒業。ノースカロライナ大学での消化器学フェローシップを経て、現在同大学の医学・微生物学・免疫学特別教授を務める。

Sartor 教授は難治性炎症性腸疾患（IBD）の治療を専門とする臨床医であるとともに、粘膜免疫学・微生物学の研究者でもあり、腸内細菌が腸粘膜の恒常性や慢性炎症に関与するメカニズムの解明に長年取り組んできた。げっ歯類の IBD モデルを用いた基礎研究を行い、IBD 患者を対象とした臨床研究に応用するトランスレーショナルリサーチを行っている。また、ノトバイオートマウスやヒト検体を用いて腸内常在細菌と遺伝的免疫応答との関係を調べ、腸内細菌の構成と機能に対する環境因子の影響について調査している。これまでに 400 以上の論文や論説を発表、5 冊の書籍を編集しており、1983 年以降アメリカ国立衛生研究所（国立糖尿病・消化器・腎疾病研究所）から継続的に研究助成を受けている。2020 年には、腸の炎症と恒常性における腸内細菌の役割に関する長年の業績が認められ、米国消化器病学会（AGA）の Basic Science Achievement Award を受賞した。また、若い科学者の育成に貢献したとして、2019 年に AGA マイクロバイオーム部門の Mentoring Award を受賞している。現在は、世界最大級のノトバイオート動物施設である UNC National Gnotobiotic Rodent Resource Center の所長および UNC Center for Gastrointestinal Biology and Disease の副所長を務める。さらに、UNC Multidisciplinary IBD Center を設立し、Crohn's and Colitis Foundation の主席医療顧問も務めた。

要約：

細菌、真菌、ウイルス、古細菌、原生動物、蠕虫などを含む多様な腸内微生物は、粘膜および全身性の免疫反応、食事成分や生体異物、薬物の代謝、そして腸管上皮の成長、発達、修復に多大な影響を与える。したがって、腸内細菌叢が消化管がんの発症や治療応答性に深く関与していることは想像に難くない。ヒト常在細菌は胃腺がん（ヘリコバクター・ピロリ菌）や大腸がん（コリバクチン産生性 PKS+ 大腸菌、バイオフィルム形成性の腸管毒素原性バクテロイデス・フラジリス、細胞内フソバクテリウム・ヌクレアタム）の発生機序に関与するほか、膵管腺がん、肝細胞がん、胆管がんとの関連も示されており、真菌については食道扁平上皮がんとの関連が指摘されている。さらに腸内細菌叢は、薬物代謝、免疫応答、がん細胞の化学療法抵抗性などを変化させることで、治療の成果に影響を及ぼす。例えば、腸内細菌のβグルクロニダーゼ活性を阻害すると、抗がん剤イリノテカンの副作用である腸粘膜炎の発症が抑制される。また、腸内細菌叢は、膵臓がんを含む様々ながんの免疫チェックポイント阻害剤に対する応答に大きく影響する。腸内細菌叢プロファイリングを行うことで、がん免疫療法の治療効果、転帰、合併症リスクを予測することができる。抗生物質、糞便移植、または特定の微生物コンソーシアや製品の投与により腸内

細菌叢を変化させることで、がんの治療効果を高めることができるとのエビデンスも蓄積されつつある。ディープシーケンシングやメタボローム解析によって患者一人一人の腸内細菌構成や機能を把握することで、個人に合わせた治療法の選択や様々な薬剤に対する治療効果と副作用の予測を可能にし、治療結果を大幅に改善できる可能性が考えられる。究極的には、遺伝子解析や菌叢解析により高リスク群と診断された人に対して食生活や環境リスク因子と合わせて腸内細菌叢を操作することで、がんの発症率を低減できることが期待される。

参考文献

1. Sepich-Poore GD, Zitvogel L, Straussman R, Hasty J, Wargo JA, Knight R. The microbiome and human cancer. Science. 2021 Mar 26;371（6536）: eabc4552. doi: 10.1126/science.abc4552. PMID: 33766858; PMCID: PMC8767999.
2. Bhatt AP, Sartor RB. Bugs on drugs: implications for gut health. Nat Rev Gastroenterol Hepatol. 2021 May;18（5）:287-288. doi: 10.1038/s41575-021-00437-1. PMID: 33692569.
3. Arthur JC, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Fan TJ, Campbell BJ, Abujamel T, Dogan B, Rogers AB, Rhodes JM, Stintzi A, Simpson KW, Hansen JJ, Keku TO, Fodor AA, Jobin C. Intestinal inflammation targets cancer-inducing activity of the microbiota. Science. 2012 Oct 5;338（6103）:120-3. doi: 10.1126/science.1224820. Epub 2012 Aug 16. PMID: 22903521; PMCID: PMC3645302.
4. Bhatt AP, Pellock SJ, Biernat KA, Walton WG, Wallace BD, Creekmore BC, Letertre MM, Swann JR, Wilson ID, Roques JR, Darr DB, Bailey ST, Montgomery SA, Roach JM, Azcarate-Peril MA, Sartor RB, Gharaibeh RZ, Bultman SJ, Redinbo MR. Targeted inhibition of gut bacterial β -glucuronidase activity enhances anticancer drug efficacy. Proc Natl Acad Sci U S A. 2020 Mar 31;117（13）:7374-7381. doi: 10.1073/pnas.1918095117. Epub 2020 Mar 13. PMID: 32170007; PMCID: PMC7132129.
5. Awoniyi M SR, Montgomery S, Ngo B, Sartor RBS. Accelerted onset of spontaneous proximal colonic dysplasia and invasive adenocarcinoma in novel PSC-IBD model. Digestive Disease Week. Volume 615. San Diego, CA, 2019.

Intestinal microbiota and carcinogenesis: mechanisms and opportunities

Ryan Balfour Sartor
University of North Carolina — Chapel Hill, USA

Brief curriculum vitae:

Dr. Sartor was born in Shreveport, Louisiana, USA. He graduated from Washington & Lee University, Lexington, Virginia and Baylor College of Medicine, Houston, Texas, then performed a clinical and research Gastroenterology Fellowship at the University of North Carolina, where he is the Midget Distinguished Professor of Medicine, Microbiology and Immunology.

Dr. Sartor is a physician-scientist, board-certified Gastroenterologist with expertise in managing difficult-to-treat patients with inflammatory bowel diseases (IBD) and a mucosal immunologist/microbiologist with a long-term interest in understanding mechanisms by which resident microbiota induce chronic intestinal inflammation vs. mucosal homeostasis. His research develops and studies rodent models of chronic, immune-mediated intestinal inflammation relevant to IBD and performs clinically relevant translational studies involving IBD patients. He investigates genetically-determined immune responses to luminal resident microbial components using gnotobiotic mice and patient-derived samples, and studies the influence of environmental factors on intestinal microbiota composition and function. He has published over 400 articles, editorials, and chapters, edited 5 books, and have been continuously funded by the NIH (NIDDK) since 1983. In 2020, he received the American Gastroenterology Association (AGA) Basic Science Achievement Award, recognizing his career-long contributions to understanding the role of the gut microbiota in intestinal inflammation and homeostasis. His interest and success in guiding the careers of young scientists was recognized by the AGA Microbiome Section's Mentoring Award in 2019. He directs the UNC National Gnotobiotic Rodent Resource Center, one of the world's largest gnotobiotic animal facilities. and is co-Director of the UNC Center for Gastrointestinal Biology and Disease. In addition, he founded and directed the UNC Multidisciplinary IBD Center and previously served as the Crohn's and Colitis Foundation's Chief Medical Advisor.

Abstract :

The diverse elements of the intestinal microbiota, which include bacteria, fungi, viruses, archaea, protozoa and helminths, profoundly regulate mucosal and systemic immune responses; metabolize dietary components, xenobiotic compounds and drugs; and influence intestinal epithelial growth, development and repair. Therefore, it is not surprising that the gut microbiota have been strongly implicated in gastrointestinal carcinogenesis and treatment responses. Resident bacteria have been mechanistically implicated in the development of gastric adenocarcinoma (*Helicobacter pylori*), colorectal cancer (PKS^+ colibactin-producing *Escherichia coli*, biofilm-inducing enterotoxigenic *Bacteroides fragilis* and intracellular *Fusobacterium nucleatum*) and associated with pancreatic ductular adenocarcinoma, hepatocellular cancer and

cholangiocarcinoma, while fungi have been associated with esophageal squamous cell cancer. In addition, the intestinal microbiota influence the outcomes of therapy by variably metabolizing of therapeutic agents, modulating immune responses and altering chemo-resistance of cancer cells. An example of influencing chemotherapeutic responses is the inactivation of mucositis-inducing irinotecans by blocking gut bacterial β-glucuronidase activity. Intestinal microbiota profoundly influence responses to checkpoint inhibiting immunotherapy of various cancers, including pancreatic cancer. Moreover, intestinal microbial profiling can predict therapeutic responses to immunotherapy, disease outcomes and the risk of developing complications. Finally, developing evidence indicates that altering the microbiome can improve therapeutic efficacy by antibiotics, fecal transplant and potentially by defined microbial consortia or products. Understanding an individual patient's microbial signature composition and function by deep sequencing and metabolomic profiling has the potential to profoundly improve therapeutic outcomes by personalizing treatment choices, predicting therapeutic responses to various agents and decreasing drug toxicities. The ultimate hope is that manipulating the microbiome in concert with altering the diet and modifying environmental risk factors can decrease the likelihood of developing cancer in high risk individuals, as determined by microbial and genetic screening.

References

1. Sepich-Poore GD, Zitvogel L, Straussman R, Hasty J, Wargo JA, Knight R. The microbiome and human cancer. Science. 2021 Mar 26;371 (6536): eabc4552. doi: 10.1126/science.abc4552. PMID: 33766858; PMCID: PMC8767999.
2. Bhatt AP, Sartor RB. Bugs on drugs: implications for gut health. Nat Rev Gastroenterol Hepatol. 2021 May;18 (5):287-288. doi: 10.1038/s41575-021-00437-1. PMID: 33692569.
3. Arthur JC, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Fan TJ, Campbell BJ, Abujamel T, Dogan B, Rogers AB, Rhodes JM, Stintzi A, Simpson KW, Hansen JJ, Keku TO, Fodor AA, Jobin C. Intestinal inflammation targets cancer-inducing activity of the microbiota. Science. 2012 Oct 5;338 (6103):120-3. doi: 10.1126/science.1224820. Epub 2012 Aug 16. PMID: 22903521; PMCID: PMC3645302.
4. Bhatt AP, Pellock SJ, Biernat KA, Walton WG, Wallace BD, Creekmore BC, Letertre MM, Swann JR, Wilson ID, Roques JR, Darr DB, Bailey ST, Montgomery SA, Roach JM, Azcarate-Peril MA, Sartor RB, Gharaibeh RZ, Bultman SJ, Redinbo MR. Targeted inhibition of gut bacterial β -glucuronidase activity enhances anticancer drug efficacy. Proc Natl Acad Sci U S A. 2020 Mar 31;117 (13):7374-7381. doi: 10.1073/pnas.1918095117. Epub 2020 Mar 13. PMID: 32170007; PMCID: PMC7132129.
5. Awoniyi M SR, Montgomery S, Ngo B, Sartor RBS. Accelerted onset of spontaneous proximal colonic dysplasia and invasive adenocarcinoma in novel PSC-IBD model. Digestive Disease Week. Volume 615. San Diego, CA, 2019.