Infection and Immunity Welcomes the New Microbiology

Andreas J. Bäumlér, Editor in Chief, 2017 to 2027, *Infection and Immunity*

Department of Medical Microbiology and Immunology, School of Medicine, University of California, Davis, Davis, California, USA

During the “golden age of microbiology,” the schools of Robert Koch and Louis Pasteur identified pathogenic microorganisms as the causative agents of many communicable human diseases. Koch’s postulates were essential for demonstrating that a specific microbe isolated in pure culture from a lesion of the disease could produce illness in a healthy animal, which gave rise to the concept of pathogenic microbes. These seminal contributions laid the foundation for studying how pathogenic microbes interact with their hosts, a topic that continues to fascinate microbiologists, immunologists, epidemiologists, pathologists, and clinicians alike. *Infection and Immunity* serves these disciplines by publishing new insights into mechanisms underlying host-pathogen interactions and the development of novel strategies to prevent or treat infectious diseases.

However, more than 100 years after Robert Koch and Louis Pasteur established the microbial etiology of communicable diseases, the field of microbiology is currently experiencing a second period of rapid growth and expansion, driven by the realization that changes in host-associated microbial communities might be at the root of a broad spectrum of noncommunicable human diseases. These advances follow on the heels of recent progress in high-throughput sequencing technology, which has provided a wealth of information on the human microbiome and its physiological potential. Initial work in this area established novel links between the gut microbiota, the largest microbial community inhabiting our body, and a wide variety of noncommunicable diseases, including arthritis (1), arteriosclerosis (2), obesity (3, 4), diabetes (5), colorectal cancer (6, 7), liver cancer (8), asthma (9, 10), and neurodevelopmental disorders (11), to name just a few. As a result, we are today in the midst of a “renaissance in microbiology,” the inclusion of which necessitates an expansion in the scope of *Infection and Immunity* from our traditional focus on how pathogenic microbes interact with the immune system to embrace a broader view of host-microbiota interactions.

The classic concept of pathogenic microbes will continue to be invaluable for studies on the pathogenesis and epidemiology of communicable diseases and also apply to some ailments associated with microbiota disruption. For example, for microbes that fail to cause disease in individuals with intact host defenses but are associated with illness in individuals with a disrupted microbiota, the traditional concept of opportunistic pathogens or pathobionts might apply. However, the limitations of this theoretical framework become apparent when considering how microbiota-derived metabolites influence human health. For instance, some metabolites generated by the gut-associated microbial community, such as short-chain fatty acids, are important for host nutrition (12), gut homeostasis (1, 13, 14), and immune development (15–20). Alterations in the community composition or changes in the intestinal environment can alter the metabolite profile generated by the gut microbiota, which in turn can predispose to diseases such as allergic asthma (9, 10). Such scenarios might include neither a pathogen nor an individual microbe but rather microbiota-derived metabolites, which might be similar between individuals even if

Accepted manuscript posted online 24

April 2017

Citation Bäumlér AJ. 2017. *Infection and Immunity* welcomes the new microbiology. *Infect Immun* 85:e00255-17. <https://doi.org/10.1128/IAI.00255-17>.

Copyright © 2017 American Society for Microbiology. All Rights Reserved.

Address correspondence to
ajbaumlér@ucdavis.edu.

The views expressed in this Editorial do not necessarily reflect the views of the journal or of ASM.

their gut-associated microbial communities do not share a single bacterial species. To include this emerging work on the microbial origin of many noncommunicable human diseases, *Infection and Immunity* will broaden its scope to invite submissions on mechanisms underlying microbiota-host interactions.

While pioneering work on census taking and predicting physiological potential helped generate a solid foundation for microbiota research, it is now time for a “new bacteriology” aimed at studying microbial physiology and gene regulation in its natural context of a host-associated community (21). This is an exciting time to be a microbial physiologist, because many of the key observations made by profiling host-associated microbial communities will find an explanation in the basic metabolic activities of the microbe and its host. A good example is gut dysbiosis, an imbalance in the gut-associated microbial community associated with conditions of intestinal inflammation (22). During homeostasis, epithelial hypoxia of the colon (23) helps maintain anaerobiosis, thereby ensuring a dominance of obligate anaerobic bacteria within the gut-associated microbial community (24). Intestinal inflammation is associated with increased epithelial oxygenation (25, 26), which disrupts anaerobiosis in the colon, thereby driving a shift of bacterial communities from obligate to facultative anaerobes (27), a microbial signature of gut dysbiosis (22). The shift toward microbial respiration during gut inflammation (28) reflects a metabolic reorientation of host epithelial cells (29). The colonic epithelium normally consumes oxygen through mitochondrial β -oxidation, which results in hypoxia (23), while a metabolic reorientation toward anaerobic glycolysis increases epithelial oxygenation (30, 31). These mechanistic insights suggest that microbial signatures identified by microbiota profiling reflect changes in bacterial metabolism, which in turn are driven by alterations in host metabolism.

The near future will likely see many more examples of changes in microbial or host physiology providing a mechanistic explanation for imbalances identified by microbiota profiling or metagenomic analysis. Eventually, this work will give rise to novel preventative or therapeutic strategies for many noncommunicable human diseases. Microbe-host interaction is at the very center of this remarkable development, which is certain to leave its mark on the biomedical research enterprise.

Infection and Immunity is enthusiastic to become part of this development by welcoming mechanistic studies on host-microbiota interactions. Our scope statement has been modified to include such studies; *Infection and Immunity* provides new insights into the interactions between bacteria, fungi, and parasites and their hosts. Specific areas of interest include host cellular and immune response to microbes, molecular mechanisms of action of beneficial microbes or host-associated microbial communities, microbial pathogenesis, virulence factors, experimental models of infection, host resistance or susceptibility, and the generation of innate and adaptive immune responses.

REFERENCES

- Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F, Artis D, Xavier RJ, Teixeira MM, Mackay CR. 2009. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature* 461:1282–1286. <https://doi.org/10.1038/nature08530>.
- Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, Feldstein AE, Britt EB, Fu X, Chung YM, Wu Y, Schauer P, Smith JD, Allayee H, Tang WH, DiDonato JA, Lusis AJ, Hazen SL. 2011. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature* 472:57–63. <https://doi.org/10.1038/nature09922>.
- Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JL. 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444:1027–1031. <https://doi.org/10.1038/nature05414>.
- Henao-Mejia J, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, Thaiss CA, Kau AL, Eisenbarth SC, Jurczak MJ, Camporez JP, Shulman GI, Gordon JL, Hoffman HM, Flavell RA. 2012. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. *Nature* 482:179–185. <https://doi.org/10.1038/nature10809>.
- Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R. 2008. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 57:1470–1481. <https://doi.org/10.2337/db07-1403>.
- Castellari M, Warren RL, Freeman JD, Dreolini L, Krzywinski M, Strauss J, Barnes R, Watson P, Allen-Vercoe E, Moore RA, Holt RA. 2012. *Fusobacterium nucleatum* infection is prevalent in human colorectal carcinoma. *Genome Res* 22:299–306. <https://doi.org/10.1101/gr.126516.111>.
- Kostic AD, Gevers D, Pedamallu CS, Michaud M, Duke F, Earl AM, Ojesina AI, Jung J, Bass AJ, Tabernero J, Baselga J, Liu C, Shivdasani RA, Ogino S, Birren BW, Huttenhower C, Garrett WS, Meyerson M. 2012. Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma. *Genome Res* 22:292–298. <https://doi.org/10.1101/gr.126573.111>.
- Yoshimoto S, Loo TM, Atarashi K, Kanda H, Sato S, Oyadomari S, Iwakura Y, Oshima K, Morita H, Hattori M, Honda K, Ishikawa Y, Hara E, Ohtani N. 2013. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. *Nature* 499:97–101. <https://doi.org/10.1038/nature12347>.
- Russell SL, Gold MJ, Hartmann M, Willing BP, Thorson L, Wlodarska M,

- Gill N, Blanchet MR, Mohn WW, McNagny KM, Finlay BB. 2012. Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. *EMBO Rep* 13:440–447. <https://doi.org/10.1038/embor.2012.32>.
10. Trompette A, Gollwitzer ES, Yadava K, Sichelstiel AK, Sprenger N, Ngombu C, Blanchard C, Junt T, Nicod LP, Harris NL, Marsland BJ. 2014. Gut microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* 155:1451–1463. <https://doi.org/10.1016/j.cell.2013.11.024>.
 11. Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, Codelli JA, Chow J, Reisman SE, Petrosino JF, Patterson PH, Mazmanian SK. 2013. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* 155:1451–1463. <https://doi.org/10.1016/j.cell.2013.11.024>.
 12. Velázquez OC, Lederer HM, Rombeau JL. 1997. Butyrate and the colonocyte. Production, absorption, metabolism, and therapeutic implications. *Adv Exp Med Biol* 427:123–134.
 13. Chang PV, Hao L, Offermanns S, Medzhitov R. 2014. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. *Proc Natl Acad Sci U S A* 111:2247–2252. <https://doi.org/10.1073/pnas.1322269111>.
 14. Singh N, Gurav A, Sivaprakasam S, Brady E, Padia R, Shi H, Thangaraju M, Prasad PD, Manicassamy S, Munn DH, Lee JR, Offermanns S, Ganapathy V. 2014. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. *Immunity* 40:128–139. <https://doi.org/10.1016/j.immuni.2013.12.007>.
 15. Millard AL, Mertes PM, Ittelet D, Villard J, Jeannesson P, Bernard J. 2002. Butyrate affects differentiation, maturation and function of human monocyte-derived dendritic cells and macrophages. *Clin Exp Immunol* 130:245–255. <https://doi.org/10.1046/j.0009-9104.2002.01977.x>.
 16. Wang B, Morinobu A, Horiuchi M, Liu J, Kumagai S. 2008. Butyrate inhibits functional differentiation of human monocyte-derived dendritic cells. *Cell Immunol* 253:54–58. <https://doi.org/10.1016/j.cellimm.2008.04.016>.
 17. Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, Momose Y, Cheng G, Yamasaki S, Saito T, Ohba Y, Taniguchi T, Takeda K, Hori S, Ivanov II, Umesaki Y, Itoh K, Honda K. 2011. Induction of colonic regulatory T cells by indigenous *Clostridium* species. *Science* 331:337–341. <https://doi.org/10.1126/science.1198469>.
 18. Arpaia N, Campbell C, Fan X, Dikly S, van der Veeken J, deRoos P, Liu H, Cross JR, Pfeffer K, Coffey PJ, Rudenski AY. 2013. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* 504:451–455. <https://doi.org/10.1038/nature12726>.
 19. Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, Nakanishi Y, Uetake C, Kato K, Kato T, Takahashi M, Fukuda NN, Murakami S, Miyauchi E, Hino S, Atarashi K, Onawa S, Fujimura Y, Lockett T, Clarke JM, Topping DL, Tomita M, Hori S, Ohara O, Morita T, Koseki H, Kikuchi J, Honda K, Hase K, Ohno H. 2013. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* 504:446–450. <https://doi.org/10.1038/nature12721>.
 20. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly YM, Glickman JN, Garrett WS. 2013. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science* 341:569–573. <https://doi.org/10.1126/science.1241165>.
 21. Pédrón T, Nigro G, Sansonetti PJ. 2016. From homeostasis to pathology: decrypting microbe-host symbiotic signals in the intestinal crypt. *Philos Trans R Soc Lond B Biol Sci* 371:20150500. <https://doi.org/10.1098/rstb.2015.0500>.
 22. Shin NR, Whon TW, Bae JW. 2015. Proteobacteria: microbial signature of dysbiosis in gut microbiota. *Trends Biotechnol* 33:496–503. <https://doi.org/10.1016/j.tibtech.2015.06.011>.
 23. Furuta GT, Turner JR, Taylor CT, Hershberg RM, Comerford K, Naravula S, Podolsky DK, Colgan SP. 2001. Hypoxia-inducible factor 1-dependent induction of intestinal trefoil factor protects barrier function during hypoxia. *J Exp Med* 193:1027–1034. <https://doi.org/10.1084/jem.193.9.1027>.
 24. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA. 2005. Diversity of the human intestinal microbial flora. *Science* 308:1635–1638. <https://doi.org/10.1126/science.1110591>.
 25. Rivera-Chávez F, Zhang LF, Faber F, Lopez CA, Byndloss MX, Olsan EE, Xu G, Velázquez EM, Lebrilla CB, Winter SE, Bäuml AJ. 2016. Depletion of butyrate-producing clostridia from the gut microbiota drives an aerobic luminal expansion of *Salmonella*. *Cell Host Microbe* 19:443–454. <https://doi.org/10.1016/j.chom.2016.03.004>.
 26. Lopez CA, Miller BM, Rivera-Chávez F, Velázquez EM, Byndloss MX, Chávez-Arroyo A, Lokken KL, Tsois RM, Winter SE, Bäuml AJ. 2016. Virulence factors enhance *Citrobacter rodentium* expansion through aerobic respiration. *Science* 353:1249–1253. <https://doi.org/10.1126/science.aag3042>.
 27. Rigottier-Gois L. 2013. Dysbiosis in inflammatory bowel diseases: the oxygen hypothesis. *ISME J* 7:1256–1261. <https://doi.org/10.1038/ismej.2013.80>.
 28. Hughes ER, Winter MG, Duerkop BA, Spiga L, Furtado de Carvalho T, Zhu W, Gillis CC, Buttner L, Smoot MP, Behrendt CL, Cherry S, Santos RL, Hooper LV, Winter SE. 2017. Microbial respiration and formate oxidation as metabolic signatures of inflammation-associated dysbiosis. *Cell Host Microbe* 21:208–219. <https://doi.org/10.1016/j.chom.2017.01.005>.
 29. Rivera-Chávez F, Lopez CA, Bäuml AJ. 2017. Oxygen as a driver of gut dysbiosis. *Free Radic Biol Med* 105:93–101. <https://doi.org/10.1016/j.freeradbiomed.2016.09.022>.
 30. Donohoe DR, Wali A, Brylawski BP, Bultman SJ. 2012. Microbial regulation of glucose metabolism and cell-cycle progression in mammalian colonocytes. *PLoS One* 7:e46589. <https://doi.org/10.1371/journal.pone.0046589>.
 31. Kelly CJ, Zheng L, Campbell EL, Saeedi B, Scholz CC, Bayless AJ, Wilson KE, Glover LE, Kominsky DJ, Magnuson A, Weir TL, Ehrentauf SF, Pickel C, Kuhn KA, Lanis JM, Nguyen V, Taylor CT, Colgan SP. 2015. Crosstalk between microbiota-derived short-chain fatty acids and intestinal epithelial HIF augments tissue barrier function. *Cell Host Microbe* 17:662–671. <https://doi.org/10.1016/j.chom.2015.03.005>.