From cell biology to the microbiome: An intentional infinite loop

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Cell biology is the study of the structure and function of the unit or units of living organisms. Enabled by current and evolving technologies, cell biologists today are embracing new scientific challenges that span many disciplines. The eclectic nature of cell biology is core to its future and remains its enduring legacy.

As an undergraduate student, my answer to the question "what is cell biology?" was fairly textbook. Cell biology is the study of the structure and function of the unit or units of living organisms. Intrinsic to the question of what is cell biology today is the more fun and engaging question: what are the open challenges for cell biologists, particularly regarding the emergence of fields such as microbiome studies. Here I outline one open challenge: deciphering the complex interactions between commensal microbiomes and host tissue.

While I was in college, I would have said the most exciting questions in cell biology focused on organelle biogenesis and that the ultimate challenge for cell biology was to assemble a nucleus, endoplasmic reticulum, or endolysosome in a test tube. The shine hasn't faded from these questions for me, but graduate school provided me with a reality check into the complexity of such undertakings.

Yale's Cell Biology and Immunobiology departments, and the faculty there that mentored me—Ira Mellman, Jorge Galan, Peter Cresswell, and Norma Andrews, whose expertise spans cell biology, immunology, and host–pathogen interactions—influenced the questions that fascinated me during graduate school and beyond. As a graduate student in the Mellman laboratory, I studied macropinocytosis and how dendritic cells developmentally regulate this form of endocytosis to control antigen uptake. Findings from Alan Hall's laboratory that Rho GTPases regulate cell migration, morphogenesis, and polarity (Caron and Hall, 1998) and from Jorge Galan's laboratory that *Salmonella* type III effectors regulate host Rho GTPases for invasion of the intestinal epithelium (Chen et al., 1996; Hardt et al., 1998; Fu and Galán, 1999) suggested that *Salmonella* might shed light on how dendritic cells control their own membrane ruffling and macropinocytosis. With Ira and Jorge's mentorship and the use of *Salmonella* mutants and microinjection, we gained some insights into how dendritic cells use the Rho GTPase, Cdc42, to developmentally regulate endocytosis (Garrett et al., 2000).

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These salmonella experiments were the start of my interest in transkingdom relationships. Bacteria have taught and continue to teach me about cell biology and immunology. For my postdoctoral work, I had the privilege to train with Laurie Glimcher, whose laboratory has made seminal discoveries in the molecular pathways that regulate CD4 T helper cell development and activation as well as the molecular pathogenesis of osteoporosis. I came to her laboratory to deepen my knowledge of immunology and mouse models. Her scientific fearlessness and incisive intellect nurtured my developing interests in the gut microbiota. I was fortunate to receive additional mentorship from two microbiota innovators and experts, Jeffrey I. Gordon and Andy Onderdonk, during my postdoc years. The fields that I studied as a graduate student and postdoc and the expertise of my mentors spanned cell biology, biochemistry, host–pathogen interaction, microbiome studies, cancer biology, and immunology. These exposures and broad training are reflected in the wide range of scientific questions that my laboratory tries to study. The questions that stoked my interest in cell biology (e.g., how organelles assemble and maintain their size and shape) are quite similar to the questions that sparked my interest in the gut microbiota: e.g., how does a gut microbiome assemble; what factors shape its size, composition, and organization; and how does it change in response to a perturbations like food, antibiotics, immunotherapy, infections, or aging of its host? The gut microbiota is in many respects a multicellular network and has even been referred to as a "forgotten organ." Bacteria, archaea, and fungi are all cells, but is the study of the microbiota cell biology? For me this raises the question of when cell biology emerged as a discipline.

Susumu Ito, professor emeritus at Harvard Medical School, who has had a career in cell biology that has spanned more than six decades, told me that in the 1970s, departments of cell biology were born from departments of anatomy and physiology. Just as cell biology emerged from these fields, it is continuing to change with the times. More recently, systems biology departments have emerged and often are enriched with cell biologists. Synthetic biology appears to be the next wave that is sweeping up many cell biologists. These shifts in cell biology mirror the many complementary conceptualizations of the microbiota—a tunable, engineered circuit or network, a compartmentalized cell, and an organ (Fig. 1).

Given a definition of cell biology as the study of the structure and function of the unit or units of living organisms, perhaps those among us engaged in microbiome studies may find an academic

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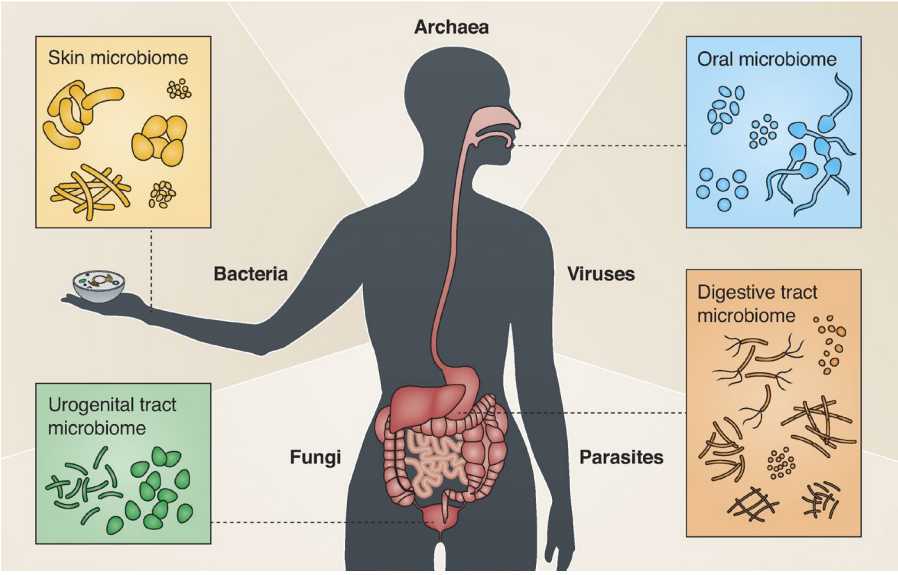

Figure 1. **The human microbiome.** Illustration depicting the diversity of the human body's microbiomes at their respective body sites. The outstretched hand reaching for the cell symbolizes the potential of cell biology to enrich microbiome studies.

home of our own within cell biology. Microbes are cells that are part of many multicellular organisms and are important for optimal organismal function. Cell biology via microscopy has brought and continues to afford a nuanced understanding of cellular processes in real time. I have similar hopes for microscopy and the gut microbiota. Fluorescence microscopy–based approaches using probes that detect microbial community members via specific regions of their DNA have been useful tools to visualize bacterial and fungal communities at surfaces, as have electron microscopy–based methods. Flow cytometry and fluorescence-activated cell sorting, which, for me, are close cousins of microscopy, are increasingly being used to "visualize" bacterial community membership, especially in conjunction with downstream techniques from single cell sequencing to defining transcriptional activity. There remain ample opportunities for innovation in bringing cell biology methods and approaches inclusive of microscopy to microbiome studies.

There are ever-present homeostatic challenges to cells or multicellular organisms at environmental boundaries. Liminal spaces like body surfaces (skin, oropharynx, gastrointestinal, respiratory, and urogenital tracts) are boundaries between host and microbe and are therefore particularly appealing from a cell biology perspective, and ripe for microbiome studies. In many animals, such surfaces are composed of polarized cells. The biology that supports the apical and basolateral architecture of intestinal epithelial cells encompasses the cell biological disciplines of vesicular trafficking, membrane transport, cytoskeletal systems, and cell–cell communication. That a polarized intestinal epithelium and its mucus layer enable the coexistence of billions of bacteria and millions of innate and adaptive immune cells within a distance of <0.1 mm remains mesmerizing to me.

There are many cell biology opportunities in defining these boundary spaces. For example, there are many unknowns in the assembly and maintenance of the intestinal mucus layer and the canonical and noncanonical roles of goblet cells, the mucus-producing cells of the intestine. From the microbial perspective, the influence of microbial products, both structural components and metabolites, on the function of epithelial and nonepithelial cells is an active area of microbiome studies with ample opportunities for cell biologists. My laboratory has interests in microbial metabolites that influence innate and adaptive immune function as well host molecules (metabolites and hormones) that affect bacterial cell function. There are also significant gaps in our understanding of how bacterial consortia assemble on body surfaces like the intestinal mucosa into so-called biofilms and the nature of host–microbe and microbe–microbe interactions in these spaces. These systems are rich areas for investigation by cell biologists that enjoy studying cell–cell interactions. Equally exciting are single cell biology questions, speculating how microbes may have influenced the architecture of cells beyond the mitochondrial endosymbiotic theory. Such questions may lead one to wax philosophical, but these are exciting challenges to tease apart given coevolution and coadaptation across the kingdoms of life. Whether one's research focus rests within the interior of a cell or comes from the outside of cells looking in, it is all cell biology.

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