

## Briefly Focus on Animal Models

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### Description

Physiology is the scientific discipline that focuses on the body's capacity to regulate its internal environment by studying individual organ functions, organ-to-organ communication, and systemic regulation. One hundred and sixty years ago, Claude Bernard proposed the concept of an "internal milieu" ensuring the stability of organ functions whereby external variations are compensated for and equilibrated. This notion led to the emergence of the concept of "physiological homeostasis," in which organic processes regulate the maintenance of steady states in the body. It was later recognized that signals arising from the changing environments where animals live interact with the body's various homeostatic systems, ultimately resulting in different physiological and biological outcomes.

Among such environmental factors, nutrition is paramount in shaping all aspects of biology, from cellular and physiological processes to behavioral and ecological interactions. In addition, the influence of the intestinal microbial communities, or the microbiota, on animal physiology and behavior is now widely recognized. Since diet and nutrition shape not only animal physiology but also the ecology of the gut microbiota, it raises the question of how the nutritional environment and microbial assemblages together affect animal physiology. These relationships are made more complex by the fact that the microbiota are themselves part of the animal's nutritional environment, serving as both a supply and a drain on the host's nutrition, thereby potentially altering the host's feeding behavior and physiology directly and indirectly. This research field is still in its infancy and we believe it constitutes a new frontier in the field of organismal biology in need of a unifying vision and guidelines.

### Bacterivorous Worm

*Caenorhabditis elegans* has proven instrumental in delineating conserved genetic pathways, characterizing novel genes, and identifying novel gene functions. The simple body plan, invariant pattern of somatic cell division and transparent body allow for the characterization of many phenotypes without the need for dissection or extensive sample processing. Although evolutionarily distant from humans, *C. elegans* and humans share many conserved cellular pathways. Notably, insulin and TOR pathways function in *C. elegans*, as in other

organisms, to coordinate nutrient and metabolic state with cellular processes.

In this context, a conference was organized on April 25–29, 2016, hosted by the Fondation des Treilles at the Domaine des Treilles in Tourtour, France. We discussed the emerging links and interdependencies among the topics of animal nutrition, microbiota, growth, metabolism, and health. At the meeting, we explored a vision for a research program in integrative physiology that aims to define and delineate the complex interactions comprising the "host physiology-nutrition-microbiota" axis. The research field studying these interrelationships is relatively young, but some impressive progress has been made at the level of phenomenological studies. We recognize the need for sophisticated descriptions of such phenomena, and for an increasing emphasis on underlying mechanisms to propel the field from correlational observations to causal links.

We believe the use of model organisms has played, and will continue to play, a decisive role in this challenge.

For *C. elegans*, bacteria are both diet and microbiota. *C. elegans* are bacterivores that can survive on a variety of bacterial species. These bacteria influence metabolism, life history traits, and gene expression. However, not all bacterial strains can colonize the animal. The microbiome of wild *C. elegans* is largely composed of proteobacteria but includes a phylogenetically diverse set of microorganisms. Sampling of animals from different geographical locations revealed a common core microbiota that differs in bacterial representation from surrounding soils, and from the microbiota of related species of *Caenorhabditis*, *C. remanei*, isolated from the same sites. Similarly, a core microbiota and two identifiable enterotypes were established in laboratory strains of *C. elegans* exposed to diverse laboratory-generated bacterial environments. Altogether, these studies demonstrate that colonization is not determined solely by the prevalence of bacterial species in the environment, but is a guided process that is likely driven by the interaction of host and bacterial factors.

### The Commensal Fly

*Drosophila melanogaster* has a long and illustrious career as a model organism to evaluate the host-pathogen interaction and

how such interactions affect host development and physiology. For example, the past research in *Drosophila* led to the identification of a novel role of the Toll receptor in innate immunity, which rapidly catalyzed the discovery of the Toll-like receptor (TLR) in humans. Now, this simple and genetically tractable model animal is actively contributing to the understanding of “animal-gut microbiota-nutrition” interactions. In addition to its powerful genetic toolkit, the fly model offers the decisive advantage of having a simple and culturable microbiota comprising approximately 20 strains mainly from the families Acetobacteraceae and Lactobacillaceae. Such low diversity makes it easier not only for analyzing the changes in commensal gut community membership, but also for identifying host and/or nutritional factors capable of influencing commensal community structure. Although most *Drosophila* gut commensal species are distinct from those of humans, members of the Lactobacillaceae family have conserved probiotic effects from flies to humans. Therefore, the observations from a Lactobacilli-*Drosophila* interaction model are directly relevant for understanding the underlying mechanistic events of probiotic effects in more complex vertebrate models, including humans.

Animal models have long enabled us to identify the shared biological functions among living organisms and facilitated the discovery of conserved molecular mechanisms governing the fundamental principles of biology. While discussing the relevant angles in integrative physiology, we reached the consensus that not all models are suitable for all biological questions, and therefore emphasized the importance of choosing the appropriate model organism to study a given biological question. We also noted the feasibility of applying research findings from one model organism to another, as part of a coherent translational pathway leading to human health applications. In this Perspective, we first review recent studies using established animal models and consider future prospects for the use of such model organisms; next, we present new approaches in human studies to discover mechanisms underlying the relationships among nutrition, physiology, and the microbiota. Finally, we propose an integrative framework derived from nutritional ecology within which to define the study of the diet-physiology-microbiota system and ultimately to link it to human health and precision nutrition.