Black Death may not have been due to bacterial characteristics, but due to a combination of climate, vector dynamics, social conditions and synergistic interactions with concurrent diseases.

Analyzing another more recent pandemic, the study from an archived formalin-fixed lung autopsy specimen and from the frozen lung tissues of an Alaskan influenza victim buried in permafrost in November 1918 allowed reconstructing the 1918-1919 Spanish influenza genome. This discovery provided insight into the nature and origin of this pathogen, which caused millions of victims worldwide. Comparison of the 1918 pandemic virus with contemporary human influenza H1N1 viruses indicates that the 1918 pandemic virus was able to replicate in the absence of trypsin, and this might be one of the reasons why the virus had a uniquely high-virulence phenotype. This information may be useful to design management programs aimed at preventing other influenza epidemics and at developing future vaccines.

Science, and genetics in particular, is constantly evolving, so new methodologies will allow extracting DNA from a greater variety of materials, and improvements in sequencing technologies will provide data that will allow us to thoroughly investigate the past to better face the future.

BIOCHEMICAL ASPECTS OF SYMBIOSIS RESEARCH

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Introduction. In symbioses, the irreducible complexity of an organism is compounded by persistent symbiotic interactions with one, two, or many phylogenetically different organisms, each of which is adapted to function in the context of its partner or partners. Until recently, the molecular basis of symbiosis could be studied only on the basis of one or a few genes and their products at a time. For example, in their research on interactions between a Legionella-like bacterium and its host Amoeba proteus, Jeon and colleagues were able to correlate the reduced expression of a single host gene product, S-adenosyl methionine synthetase (SAMS), with the rapid evolution from a pathogenic to a mutualistic relationship. It is very likely that this dramatic evolutionary transition involved multiple coevolved changes in the metabolic and regulatory networks of the two organisms, but a systematic analysis of these putative changes accompanying the change in host SAMS expression was technically unrealistic at that time. Today, just 9 years later, the association in A. proteus and other fascinating symbioses can be interrogated by a range of high-throughput methods that reveal the total (or near-total) complement of a particular class of biological molecules: genes, transcripts, proteins, lipids, metabolites, etc.

The “omics” revolution of the last decade has transformed our capacity to understand symbioses at the molecular level. It is now possible, for example, to construct an inventory of the genes coded by each partner, to quantify patterns of transcription under different environmental conditions, to establish the relationship between transcript and protein abundance for every protein-coding gene, and to determine the metabolite set that makes up the metabolic pool of the interacting symbiotic partners.

The minimal output of omics is lists of genes, proteins, metabolites, etc., that are a partial or near-complete molecular catalog of an organism or symbiosis. To use omics methods to answer biological questions requires great care in experimental design and interpretation. In the second part

of this review, we discuss informatics routes that can help the researcher to make the most of omics data for symbiosis research, especially in relation to genomic and transcriptomic approaches.

The aim. To investigate ohmic approaches in symbiosis research.

Materials and methods. Experiments are used, each conducted on a single type of animal-microbe symbiosis. In different ways, using genomic, transcriptomic, proteomic, and metabolomic data, these studies illustrate how omics approaches can be applied to answer specific questions in symbiosis research.

Research results. Our exemplar of genomics in symbiosis research is a set of papers by McCutcheon and Moran describing the genomes of the symbiotic bacteria in three related groups of xylem-feeding insects: the Cercopidae (spittlebugs), Cicadoidae (cicadas), and Cicadellinae (sharpshooters). All three insect groups bear two morphologically distinct bacterial symbionts: a common primary symbiont (Sulcia mulleri) and a distinct auxiliary symbiont. Plant xylem sap lacks the 10 essential amino acids that animals cannot synthesize but require for protein synthesis. Genomic inspection of the primary and auxiliary symbionts revealed that Sulcia has the genetic capacity to synthesize either 7 (in spittlebugs) or 8 (in cicadas and sharpshooters) essential amino acids, and that the auxiliary symbionts encode the biosynthetic pathways for the remaining essential amino acids; thus, the various auxiliary symbionts and the cohabiting Sulcia have perfect complementarity in their genetic capacity for essential amino acid synthesis. These studies demonstrate how the genome of each bacterial symbiont is shaped by coevolutionary interactions with symbiotic partners. Furthermore, they generate very specific predictions about the three-way transfer of multiple metabolites (including essential amino acids) among the host and symbionts.

As these studies illustrate, metabolic interactions in symbioses can be inferred by visual inspection of genomic data. Nevertheless, the metabolic networks are inherently complex, even in bacteria with reduced genomes, and metabolic modelling based on the inventory of metabolism genes offers a valuable route to identify and quantify the nutritional resources utilized by the symbiotic bacteria and their metabolic adaptations for the release of specific nutrients to the host. These methods have been applied with success, for example, to the endosymbionts of aphids, sharpshooters, and cockroaches. This approach is ideally suited to bacteria with much reduced genomes, in which all metabolism-related genes are expressed. For many bacteria, however, the metabolic phenotype under any one set of conditions is underpinned by a subset of the metabolism-related genes. For these bacteria, it is essential to complement the genomic information with gene expression data.

Phylogenomics allocates genes according to their evolutionary history, with the rationale that genes with a similar evolutionary history will cluster according to function. This technique is particularly valuable to generate candidate functions for genes lacking functional annotation. Gene evolutionary history is predicted by creating a coinheritance matrix of all the proteins in the genome sequence of interest (rows) against a library of genomes.

Phylogenomics is particularly well-suited for functional inference of genes in bacteria because many sequenced bacterial genomes are available to support the analysis. Phylogenomics has been applied recently in combination with filtering approaches to identify putative symbiosis-related genes of Xenorhabdus nematophila and X. bovienii, bacterial symbionts of entomopathogenic nematodes.

To date, the symbiosis community has apparently made little use of transcriptional network analysis, but we anticipate that this will change rapidly in the next few years. One recent study that does apply gene networks to the study of symbiosis investigated the transcriptional responses of humans to probiotic Lactobacillus. The same human subjects were separately exposed to each of three

probiotic Lactobacillus species. The microarray data were highly variable across individuals: transcriptional responses were more similar for different treatments on the same individual than for the same treatments on different individuals. Nevertheless, network analysis of the transcriptomes identified a number of networks that responded to the different Lactobacillus species, and certain networks that responded to more than one of the probiotic bacteria. Although the actual transcriptional levels varied among individuals across the study, the network responses appeared to be conserved, allowing interrogation of what otherwise seemed to be a near-uninterpretable dataset.

Although the regulatory networks described in Van Baarlen were not created from transcriptomic data (instead, networks were created by combing the literature for experimental data), they demonstrate the power of gene network discovery for analysis of large transcriptomic datasets in symbiotic systems. Network creation from transcriptomic data has recently been used to study mammalian gastrointestinal symbiotic systems, and has also been used successfully, sometimes with experimental verification, with transcriptomic data in a variety of organisms.

Conclusions. Omics approaches are taking our understanding of symbioses to a new level of molecular sophistication. Indeed, the monumental efforts to define and characterize human-associated microbial communities by initiatives such as the Human Microbiome Project are attainable only by implementation of omics methods. Some types of interactions, such as regulation of the nutritional status and cell proliferation patterns of the host, make intuitive sense, but interpreting other results of omics experiments will require further research on the function of certain gene classes. For example, one-third of the proteins that differ in abundance between pea aphids bearing and experimentally deprived of their Buchnera bacteria are cuticular proteins, a result that cannot be related to any currently known aphid-Buchnera interaction. As this result illustrates, omics experiments have great potential to spur efforts to understand molecular function in symbiosis.

From a symbiotic perspective, gene classes of particular potential interest are those that respond specifically to perturbation of the symbiosis and have no known function. Conserved genes of this class may represent the deep history that defines the predisposition of animals for symbioses with microorganisms, while recently evolved, lineage-specific genes may underpin the unique functions of individual associations. Elucidation of these patterns will contribute not only to our understanding of symbiosis, but also to the resolution of central problems posed by conserved and lineage-specific genes of no known function.

BIOCHEMICAL INDICATORS IN ADRENAL DISORDERS IN THE BACKGROUND OF LIVER CIRRHOSIS

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Introduction. Hypoproteinaemia states represent a challenge when assessing hypothalamus-pituitary-adrenal (HPA) axis functionality. This scenario is common in cirrhosis and further complicated by significant overlap between clinical manifestations of adrenal insufficiency (AI) and decompensated liver disease. Additionally, AI exists along a spectrum in patients with cirrhosis and