

Extreme Excitement about Archaea

Dark Matter of Our Microbiome



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40 years ago, Woese and Fox described the tree of life as we know it today, with three branches representing Eukaryota, Bacteria, and Archaea. In the last few decades, important findings have shaken our picture of the ecology and importance of archaea and have revealed novel traits beyond archaeal extremophily and supposed “primitiveness.” However, archaea are not only environmentally important microorganisms: they are also substantial components, or even keystone species, in complex plant, animal, and human microbiomes. Archaea have been constantly overlooked in the human microbiome—or not considered important enough, as no pathogenic archaeon has yet been identified. Since archaeal biology is fundamentally different from that of bacteria, we face numerous methodological problems to properly assess their diversity, abundance, metabolism, and structure. As long as scientists hesitate to increase their efforts to assess the archaeome along with the bacteriome, we miss a big part of the microbiome. Single methanogenic archaeal species can easily reach up to 10% of all anaerobic microorganisms in the gastrointestinal tract, outnumbering the most abundant bacterial species we have identified thus far. Besides the gut, known and novel archaea thrive in the oral and vaginal cavities, on the skin, and in the lungs. Discovering this unexpected diversity of archaea interacting so closely with us, I was once more completely overwhelmed and surprised by this fascinating domain of life, which appears to have found a lifestyle dedicated to syntrophy and mostly positive interactions—at least until we identify the first archaeal pathogen.

Epigenetics in Boiling Acid



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Life in boiling acid: how do they do it? Thus began my exploration into the world of archaea inhabiting acidic hot springs. My interest in an astounding biological phenotype drove me to nutrition, gene expression, and metal resistance. Because each offered up unprecedented biology (and a continuing refrain of “not like bacteria”), I was encouraged to move on to the use of adaptive laboratory evolution to really test the limits of hot-acid resistance. The resulting organisms became drastically more acid resistant than any known natural isolate. Many assumed this would have arisen by mutation, but no genetic changes could explain the phenomenon. Instead, these archaea (a genus called *Sulfolobus*) use something new and something like epigenetics: heritable patterns of gene expression that change without altering DNA sequence. It turned out that DNA-bound proteins had lost post-translational modification, much like our histones do when we undergo epigenetic changes. While this may seem commonplace in eukaryotic biology, epigenetic control of this variety in the archaeal domain may have major implications for understanding the evolution of gene-expression control. Excitement is all around us now as this story unfolds. Archaea are wonderful, instructive, and truly motivating creatures that will continue to provide stimulating careers to the next generation of scientists.

The Original Parasites?



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One of the most intriguing results of the research on viral diversity on our planet is the revelation of the special nature of DNA viruses infecting archaea, particularly those thriving in extreme thermal environments at temperatures above 80°C. Unusual features of this group of viruses include incredible diversity of elaborate virion architectures—many of which have never been observed among DNA viruses of bacteria or eukaryotes—as well as their genetic content, which in some cases is literally *terra incognita*, without a single gene with homologs in extant databases. Archaeal viruses also operate through unique modes of interaction with host cells, a particularly fascinating example of which is a virion release mechanism employing special gateway structures. Archaeal viruses are remarkable due to their capacity to withstand extreme conditions that are usually destructive for nucleic acids, proteins, and lipid membranes. The biological and evolutionary underpinnings of the unusual features of archaeal viruses remain presently unclear, and understanding the molecular basis of archaeal virus stability could contribute to the development of new materials for bionanotechnological applications. It is possible that archaeal viruses represent living fossils of the ancient virosphere, which emerged at the early stages of cellular evolution and existed at the time the last universal common ancestor, and/or that some archaeal viruses evolved more recently within particular lineages of archaea. Understanding the origins of archaea-specific viruses and the basis for their host specificity promises to provide fundamental insights on the evolutionary history of virus-host interactions.



Just Keep Swimming



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Research in the archaeal field has long been restricted to biochemistry and descriptive physiology, as it was difficult to establish archaeal model systems that would be genetically accessible. However, now a number of such systems have been developed, enabling us to ask what the role of certain proteins and their interaction partners are in the respective organism. The available genetic toolboxes offer all possibilities to delete genes, insert tags, express proteins, and silence genes using CRISPR technologies. These are mainly available for different halophiles, *Sulfolobus* species, methanogens, and hyperthermophiles (*Pyrococcus* and *Thermococcus*). These tools can now be employed to understand archaeal cell biology, and a good example of this is the unique motility structure of archaea: the archaellum. Although the archaellum is a rotating structure like the flagellum of Bacteria, the structures are not evolutionarily related. The archaellum is assembled via a mechanism related to archaeal and bacterial type IV pili. In the coming years, it will be important to understand how the archaellum is rotating and especially how it is localized in the cell. The localization of the archaellum is probably influenced by components involved in cell division, which will be interesting to follow up in archaeal cell biology.

Expect the Unexpected



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The discovery of Archaea as the third domain of life has resonated through biology in a way that few others have. The unique properties of archaea have seen them viewed as ecological villains or champions. Villainy may be ascribed to methanogenic archaea, as they make a substantial biological contribution to global greenhouse gas production—although it is worth noting that human endeavor (farming ruminants) is a major driver. Contrastingly, archaea appear “friendly,” as a total of zero animal or plant diseases are known to be caused by them. Archaea are often associated with environments that humans consider extreme. As a result, archaea have inspired generations of astrobiologists to expand their horizons in the search for extra-terrestrial life and provided bountiful harvests for commercial enterprises: archaeosomes as self-adjuvanting antigen delivery vehicles, Pfu DNA polymerase for PCR, and—one can only imagine—the possibilities for archaeal CRISPR-Cas systems for genome editing. But beyond their propensity to be viewed as extremophiles—and paralleling their quintessential role in the evolution of life—functionally, archaea play roles in global biogeochemical cycles that are pivotal to the continuation of life on Earth. As beholden as we are to these discoveries, we can confidently “turn over the next rock” expecting to find nothing less than the unexpected and to revel in gaining fundamental new insight about archaea and their contributions to life on Earth.

Rewriting Protein Function



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On the topic of archaea, one might ask, “why study what seems to be essentially just a weird sort of bacteria that lives in odd places?” Historically the intrinsic value of archaea has often been based on their individual components, as they’ve been stripped for parts that can be monetized as biotechnological reagents. In the frenzy to find and sell these commodities, understanding their basic biology has been underemphasized. Their phylogenetic position makes them chimeric, sharing attributes with both bacteria and eukaryotes. This feature makes archaea the perfect models for scientists inclined to think outside the box, as their biology continually challenges the status quo of settled science. For example, as the process of protein cataloging has become pervasive, a protein is identified, and based on similarities to other known proteins, its activities are predicted and verified. Its biological function is now considered known. But is it? As we dissect the enzymes and proteins of archaea, we are finding new, previously unknown activities for some “understood” proteins. These ingenious moonlighters have multiple, autonomous functions not apparent from initial characterization. For instance, the *Sulfolobus solfataricus* TreX enzyme is a glycoside hydrolase by homology that can reshape its active site with an oligomeric state change, becoming an α -1,4-transferase. In another case, the *Thermococcus kodakarensis* fructose-1,6-bisphosphate aldolase/phosphatase uses a single active site for distinct aldolase and phosphatase activities. Clearly, archaea are underexplored opportunities for discovery, and for those with boundless curiosity, these scientific oddities may be a chance to learn something truly new.