Alfred Nobel Symposium
Energy in Cosmos, Molecules and Life
June 18-22, 2005

The Microbial Contribution to Energy in Man

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Information about the origin and evolution of life is hidden in the genetic material of modern organisms. By interpreting this information with the help of computational methods we may be able to reconstruct a view of early life and gain a deeper understanding of the coherence of all life forms.

Carl von Linne from Sweden constructed a classification system for plants already 300 years ago. Similar attempts to develop a natural classification system for microorganisms were initially met by failure. Carl Woese revolutionized these studies by collecting and comparing ribosomal RNA sequences from all types of living cells. Surprisingly, he observed that a group of microorganisms, called the archaea, had ribosomal RNA sequences as different from bacteria as from humans. Based on the comparative analysis of ribosomal RNA sequences Carl Woese constructed a natural scheme for all living organisms, called the Tree of Life that consists of three major kingdoms, the bacteria, the archaea and the eukaryotes.

In the tree of life, species are descending in a vertical manner. However, interweaved among the diverging lineages are nodes resulting from the merging of two branches at which heritable elements are transferred among parallel lines of descent. The extent at which such genetic transfers occur in nature is still an issue of much debate. In the Tree of Life, two major cross-kingdom transfer events are depicted. These are thought to derive from two separate endosymbiotic events in which bacteria fused with early versions of the eukaryotic cell. As a result, two organelles were formed that play a central role in energy recycling. The chloroplast is the site of photosynthesis whereas the function of the mitochondrion is aerobic respiration.

Human cells normally contain hundreds of mitochondria and these are of vital importance for the function of the neural and muscular systems. Mitochondria are controlled by two genomes; both their own and that of the nucleus. The genomes of mitochondria are highly variable in size, with the 16-20 kb genomes of higher eukaryotes being among the smallest. The tiny mitochondrial genomes encode only a few proteins, which are normally components of the cytochrome oxidase, cytochrome b and nicotnamide adenine dehydrogenase complexes. Mutations in mitochondrial genes often cause severe dysfunctions, including central nervous disorders, sensory neuron loss, epilepsy and dementia. Because both the mitochondria and the chloroplasts contain their own genetic material, it is possible to trace the origin of these organelles. Phylogenetic reconstructions of organellar genes suggest that the chloroplast is derived from the cyanobacteria, whereas the mitochondrion is thought to share a common ancestor with the alpha-proteobacteria.

The alpha-proteobacteria is one of the most highly abundant bacterial

subdivisions on earth, as suggested for example by environmental sequencing of the Sargasso Sea. This subdivision displays a 10-fold genome size difference and an amazing variation in lifestyles, and is an excellent model system for studies of bacterial genome evolution. The recent sequencing of some 20 alpha-proteobacterial genomes, including those of nitrogen-fixing soil-bacteria as well as of many human pathogens, such as *Rickettsia prowazekii*, the typhus pathogen, *Bartonella quintana*, the agent of trench fever and *Bartonella henselae*, the agent of cat-scratch disease, now enables a genomic comparison of the relationship between alpha-proteobacteria and mitochondria.

With the aid of computational approaches we have examined the evolution of the alpha-proteobacterial genomes. The analysis suggests that the alpha-proteobacterial ancestor contained some 3,000 to 5,000 genes and was biochemically highly versatile, with a complete system for aerobic respiration and a broad biosynthetic capability. Extreme genome size expansions of a few thousand genes have accompanied the evolution of the soil growing plant-associated bacteria. In contrast, the elimination of a few thousand genes is a characteristic feature of shifts to obligate intracellular parasitism and vector-mediated transmission pathways. The results are summarized in a model that describes the flux of genes within the alpha-proteobacteria in response to altered environmental conditions.

Based on these results, we have examined the relationships of the mitochondrial and alpha-proteoabacterial proteomes. Most of the mitochondrially encoded proteins, such as components of the NADH complex shows a strong phylogenetic relationship to the alpha-proteobacteria. However, a vast majority of mitochondrial proteins are encoded by the nuclear genome of the host and imported into the mitochondrion. Approximately half of these have bacterial homologs but do not show such a clear relationships with the alpha-proteobacteria and may possibly have been derived from earlier transfer events. Another 50% have no bacterial homologs and we have suggested that these have been added to the mitochondrial proteome subsequent to its integration with the eukaryotic cell. This suggests that the key mitochondrial enzymes involved in aerobic respiration represent bacterial innovations that were horizontally transferred to the eukaryotic cell, whereas a majority of the modern mitochondrial proteins were presumably added to the mitochondrion at a later stage.