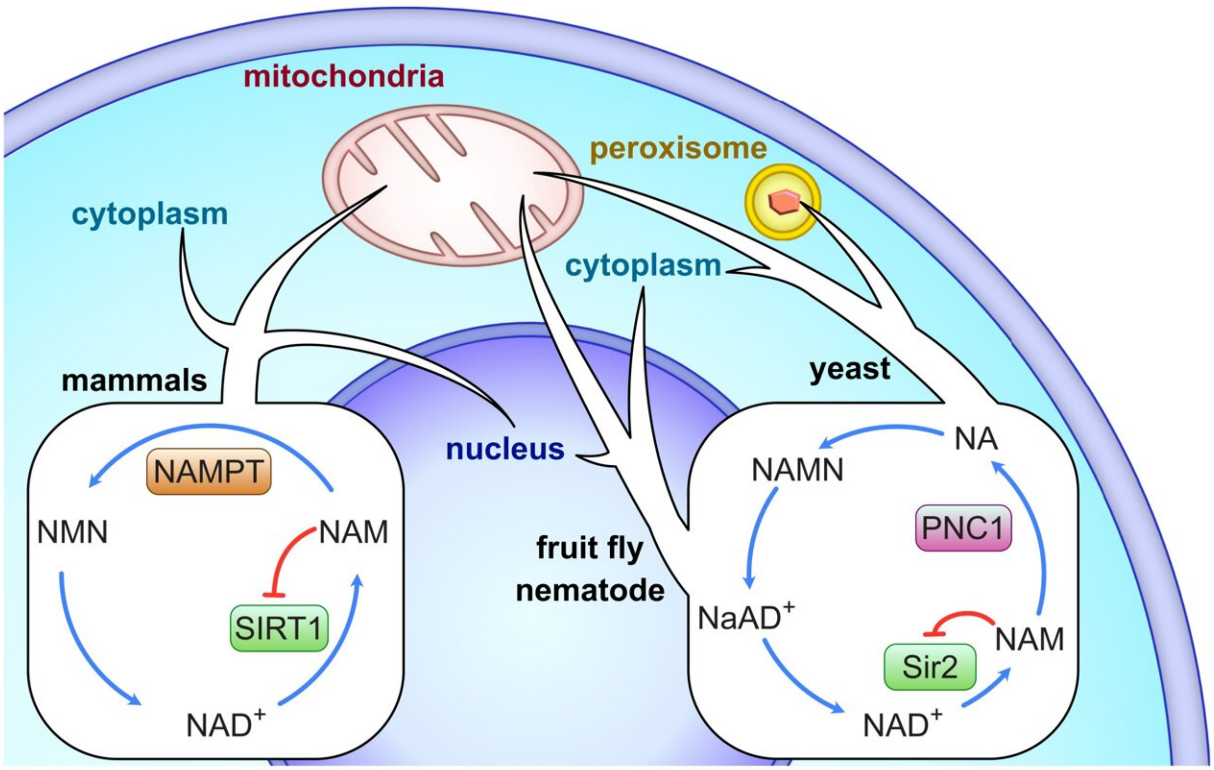
Discovering sirtuin longevity proteins in early branches of animal life

September 22 2022, by Andy Fell



Overview of the different sirtuin/NAD$^+$ pathways in model organisms, including mammals, fruit flies (Drosophila melanogaster), nematodes (Caenorhabditis elegans), and yeast (Saccharomyces cerevisiae). Arrows indicate the regions of the cell where sirtuin activity has been described in each organism. Credit: *Molecular Biology and Evolution* (2022). DOI: 10.1093/molbev/msac192

Animals on the early branches of the tree of life, such as jellyfish and sea sponges, defy the usual conventions of aging. Some show abilities to regenerate damaged or missing tissues, halt or reverse aging, and in the case of at least one jellyfish species show a form of "immortality." A new study from researchers at the University of California, Davis, and Harvard Medical School takes a detailed look at a group of proteins called sirtuins, linked to protection against cellular injury and aging, in these animals and across the rest of the animal kingdom. The work was published Sept. 6 in *Molecular Biology and Evolution*.

David Gold, assistant professor in the Department of Earth and Planetary Sciences, UC Davis College of Letters and Science; and David Sinclair, Harvard Medical School, set out to reconstruct the evolution of sirtuins with special attention to the understudied animals on life's early branches.

"The big takeaway is that there was a radiation of sirtuins early in animal evolution, with a substantial amount of loss over time. If you only look at model organisms (i.e. yeast, roundworms, fruit flies, mammals) it appears as if the number of sirtuins has increased over evolutionary time. But we describe multiple sirtuins that have not been recognized previously, which are primarily found in early branching animals like jellyfish, sea anemones, and sea sponges," Gold said.

Sinclair's laboratory originally helped discover the connection between sirtuin and aging in yeast and the connections between sirtuin proteins and longevity in mammals.

"One of my specialties is reconstructing the evolution of gene families over long timescales. So I suggested we examine the distribution of sirtuins in early animals to see if there is any correlation between sirtuin copies and their unusual longevity," Gold said.

Over 15,000 sirtuin proteins have been identified in more than 6,000 species of living things. Sirtuins are involved in metabolism of nicotinamide adenosine dinucleotide, or NAD, which plays a central role in energy metabolism, DNA repair and other vital processes inside cells. Sirtuins and NAD are involved in two main pathways, each involving a different protein, NAMPT or PNC1. NAMPT pathways are found in mammals and bacteria, while PNC1 is found in fruit flies, yeast and roundworms. Added to this, most eukaryotes have multiple versions of sirtuin.

Sirtuins appear early in evolution

Because they are so vital, sirtuins, NAMPT and PNC1 must have appeared very early in the evolution of life. But since then, they have gone through many changes and variations in the different branches of life.

Gold and Sinclair searched for sirtuin-type proteins from different animals in public databases and assembled them on an evolutionary tree. They focused on the early branching animal phyla: Porifera (sea sponges), Ctenophora (comb jellies), Placozoa (amoeba-like animals) and Cnidaria (sea anemones, corals, jellyfish and hydras).

The researchers discovered multiple new sirtuins, mostly in the early branching animals. The last common ancestor of all animals had at least nine sirtuins, they found. Since that distant time, there has been a complex pattern of gain and loss. New sirtuin genes formed from duplications of old ones. Some families of proteins disappeared in one lineage of animals but were retained in others to the present day.

The first animals had genes for both NAMPT and PNC1, but these have repeatedly disappeared from lineages. There does not appear to be any clear pattern to why a modern group of animals lost or retained either, or why it has some sirtuin protein families but not others, Gold said. Nor does there seem to be a direct link between any one particular sirtuin family and longevity, he said. However, the discovery of extra sirtuin genes in early branching animals is exciting and could play a key role in their longevity and unique life history strategies.

"We don't know what the connection is yet between these extra copies of the sirtuin gene and the unusual life histories of early branching animals. That's the next step," Gold said.

More information: David A Gold et al, Sirtuin Evolution at the Dawn of Animal Life, *Molecular Biology and Evolution* (2022). DOI: 10.1093/molbev/msac192

Provided by UC Davis