Is nature mostly a tinkerer or an inventor?

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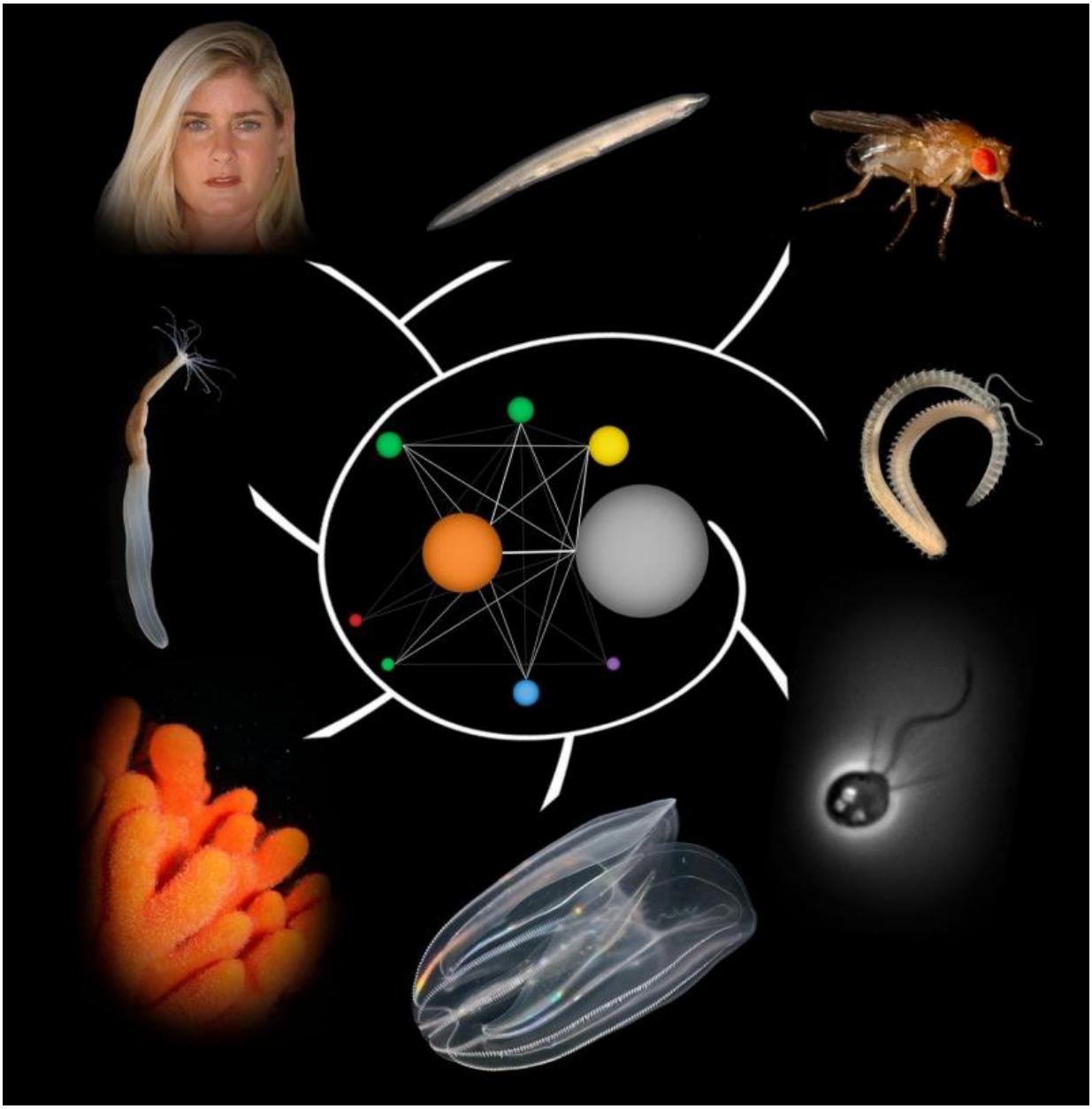

The KLF/SP protein domain co-occurrence network map is depicted in the

center. The domain network map is encircled by a phylogenetic tree depicting branching relationships for some of the phyla used in the study. Images (with photo credit) clockwise from the lower right; Monosiga brevicollis (photo by Stephan Fairclough/CC BY 2.5), Mnemiopsis leidyi (photo by William E. Browne), Echinoclathria dichotoma (photo by Pbsouthwood/CC BY 3.0), Nematostella vectensis (photo by William E. Browne), Homo sapiens (photo by William E. Browne), Branchiostoma lanceolatum (photo by Hans Hillewaert/CC BY 4.0), Drosophila melanogaster (photo by William E. Browne), and Scolelepis squamata (photo by Hans Hillewaert/CC BY 4.0).

The Krüppel-like factor and specificity protein (KLF/SP) genes are found across many species, ranging from single cell organisms to humans. This gene family has been conserved during evolution, because it plays a vital role in regulating the expression of other genes. Understanding the evolutionary history of the KLF/SP gene family may shed light on major events in animal evolution and perhaps help discern some of the molecular mechanisms associated with certain human diseases, including many cancers.

By closely examining the genomes of 48 species, biologists from the University of Miami (UM) College of Arts & Sciences have revealed the timing and mechanisms underlying the expansion and diversification of the KLF/SP gene family, which is known to regulate the maintenance of stem cells. Their study shows that, while the origin of the KLF/SP gene family predates the origins of animals well over 600 million years ago, the expansion of the gene family and increasing cell type diversity in animals happened concurrently.

"Our study paints a picture of nature innovating largely through sharing the functional bits of genes—tinkering with molecular genetic material that already exists," said William E. Browne, assistant professor of Biology at UM's College of Arts & Sciences and principal investigator of

the study.

The KLF/SP genes, like other protein coding genes, contain codes for specific combinations of protein segments called domains. To explain the relationship between genes and domains that they encode, Browne likens a gene to a sentence and domains to the words the sentence contains.

"A gene (the sentence) typically performs multiple functions and often each of those functions can be associated with a discrete domain (a word)," Browne said. "Typically a gene carries out a series of functions based upon the combination and arrangement of the discrete domains it encodes," he said. "It is this collection of domains, corresponding to functions that define a gene's 'activity' or role within a cell."

The analysis reveals that the primary mechanisms for the expansion and diversification of the KLF/SP gene family, during evolution of animals occurred as a complex intersection of domain shuffling (where segments of a gene that code for specific domains are shuffled between genes during evolution), gene duplication (the process by which an entire gene is duplicated), and de novo domain evolution (the emergence of gene sequences with novel functional protein domains).

This domain-centric approach is one of the unique aspects of the current study.

"By identifying the independent evolutionary trajectories of each domain, we were able to show that diversification of the KLF/SP gene family was accompanied by the acquisition of additional protein-protein interaction domains," said Jason S. Presnell, Biology Ph.D. student at UM's College of Arts & Sciences and first author of the study. "Most of these domains were already present in other genes and were likely acquired by KLF/SP genes via recombination."

KLF/SP genes belong to an important class of genes, called transcription factors, which either turn on or turn off the expression of other genes. The findings show a clear increase in repressor domains (domains that turn off the expression of other genes) as the KLF/SP gene family has expanded. This expansion mirrors increases in cell type diversity among animals and demonstrates that the transition from single-cell life to multicellular life occurred largely by "tinkering" with existing genes.

"This is interesting because it supports the idea that the appearance of new types of cells in a lineage of organisms as they evolve may be, more commonly, a consequence of turning off genes in unique temporal and spatial combinations," Browne said. "Large numbers of unique cell types are required to support the development of complex tissues and organs."

For the study, the researchers looked at 48 different genomes ranging from plants; single celled organisms including slime molds, fungi, and choanoflagellates; early branching multicellular animals including ctenophores, sponges, and jellyfish; invertebrates including insects and sea urchins; to vertebrates such as sharks, fish, and mammals including humans.

"This was the first study to examine the evolutionary history of the KLF/SP gene family on such a broad scale," Presnell said. "We are hopeful that our continuing experiments will help illuminate the ancestral functions of these important genes and provide some insight into the critical transition from single celled life to animal multicellularity."

The study titled "KLF/SP transcription factor family evolution: expansion, diversification, and innovation in eukaryotes" is published in the journal *Genome Biology and Evolution*. Christine E. Schnitzler from the National Human Research Institute, National Institutes of Health, is co-author of the study. The researchers are now developing strategies for

assessing the function of these genes in the comb jelly Mnemiopsis leidyi, an important model system for exploring the early evolution of animals.

Provided by University of Miami