Resolving Animal Phylogeny: A Sledgehammer for a Tough Nut?

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While great progress toward discovering the evolutionary relationships of major animal groups has been made in the past 2 decades, significant portions of the animal tree remain unresolved. A recent manuscript in Nature by Dunn and colleagues tackles this problem using massive sequence data sets from many taxa—the so-called “phylogenomic” approach.

2008 is an important anniversary for the study of the evolution of the animal kingdom. Twenty years ago (the exact date was February 12) Katharine Field and colleagues published the first comprehensive molecular phylogenetic analysis of the major groups (phyla) of animals (Field et al., 1988). The Field et al. analysis was made possible by developments in molecular biology that allowed easy sequencing of the small subunit (SSU) ribosomal RNA genes from cellular RNA. With widespread adoption of PCR, comparisons of the easily amplified SSU gene formed the basis for a series of studies of animal evolution, culminating, in the late 1990s, in what has become known as the new animal phylogeny (Adoutte et al., 2000).

It has since become clear that almost every aspect of the original Field et al. phylogeny is wrong, and while great progress has been made in the following 2 decades, major portions of the animal tree remain unresolved (Philippe and Telford, 2006). This has led some to despair of ever resolving the rapid radiations of animal phyla apparent in the Cambrian fossil record (Rokas et al., 2005). There is reason for optimism, however, and recent work using the much larger data sets made possible by genome-scale sequencing is allowing molecular systematists to address the principal problems that affect phylogenetic analyses.

Errors in phylogeny result from homoplasy in the characters used. Homoplasy occurs when unrelated taxa independently evolve an identical character through convergent evolution, which leads to the incorrect grouping of the affected taxa. In contrast, an honest phylogenetic character is shared through inheritance from a common ancestor. Homoplasy is prevalent in all molecular data sets and causes two classes of error: stochastic and systematic (Philippe and Telford, 2006).

Stochastic errors are due to small data samples, which may, by chance, contain more misleading than honest characters; this error naturally affects nodes with weak support more than those with a strong signal, but it can generally be avoided by using longer sequences or more genes.

Systematic errors occur when unrelated taxa respond similarly to selective pressures such as a shift in GC content or in rate of substitution; these shared tendencies lead to convergence and hence to homoplasy. The myriad causes of systematic error can be tackled both by accounting for the sources of error in the models of evolution used to infer trees, and by having a denser sampling of taxa. In their study, Dunn et al. (2008) have followed all three approaches for avoiding these errors in tree reconstruction: more genes, more taxa, and better models.

Considerable sequence resources exist for a little over half of the animal phyla; these data include whole genome sequences and large EST sequencing projects and have been used in previous “phylogenomic” analyses (Telford, 2007). The existing collections of sequences, however, are biased toward model organisms such as arthropods, nematodes, and chordates, and toward pests and vectors of disease.

Dunn et al. have produced considerable numbers of new sequences (almost 40 megabases); however, the most important contribution of the new analysis is in the diversity of new taxa covered by their analysis (Dunn et al., 2008). They have succeeded in collecting sufficient material to make cDNA libraries from some of the tiniest and rarest of all animal phyla, including such obscure groups as the kinorhynchs, gnathostomulids, and myzostomids. In all, they provide the first large-scale data sets for more than one-third of the 26 animal phyla represented in their tree. Significantly, only five recognized animal phyla are missing: the placozoans (of which the Trichoplax adhaerens genome is hotly anticipated), and four groups of microscopic animals—the mesozoa (parasites of octopus kidneys), micrognathozoans (recently discovered in hot springs), cyclophorans (recently discovered on lobsters’ jaws), and the loricifera (denizens of the interstices of sand grains).

Analyzing these data with the most up-to-date probabilistic models of evolution (Lartillot and Philippe, 2004), three different themes emerge with some inevitability: corroboration of older research, improved resolution where relationships were uncertain, and finally, several remaining problematic phyla.

As corroboration, their analyses strongly support the general structure of the new animal phylogeny. Several “simple” taxa (comb jellies, jellyfish, and sponges) branch off before the appearance of the large group of bilaterally symmetrical animals (Bilateria). Within the Bilateria there is a fundamental division into deuterostomes (chordates, hemichordates, echinoderms, and xenoturbellids) and protostomes (the rest of the invertebrates). The protostomes themselves are split into ecdysozoans—
including nematodes and arthropods (which undergo ecdysis or periodic molting) and lophotrochozoans such as annelid worms, mollusks, and flatworms (see Figure 1).

This support for the status quo is comforting, yet the real advances come with the increased resolution that their “many genes, many taxa” approach brings: perhaps most notably among the previously muddled lophotrochozoan phyla. Their strong support for a monophyletic group of mollusks, not seen in previous molecular analyses, should perhaps be seen as a triumph for the zoologists who long ago recognized the close affinities of taxa as distinct as snails, oysters, and octopuses.

More extraordinary is that the mollusks and annelid worms, despite sharing the classic form of spiral cleavage in the early embryo and a ciliated trochophore larva, are not sister groups. The honor of the closest relatives of the annelids is taken, instead, by the brachiopods (lamp shells) alongside their (equally surprising) closest relatives, the nemertean (ribbon) worms. The brachiopods have so little in common with the annelids that they used to be classified alongside deuterostomes such as echinoderms. Although the lophotrochozoan affinities of brachiopods were recognized a decade ago, this more precise placement should prompt a closer examination of their own ciliated larval stage for possible homology with the annelid trophosome. Indeed, this novel insight into the evolution of characteristics such as larval stages is one of the principal points of making a phylogeny.

The most obvious remaining problem is a group on the Dunn et al. tree containing taxa with little in common beyond a rapid rate of substitution. This shared bias is evident in their long branches and is known to result in a systematic error called long-branch attraction. Some of these long-branched taxa may indeed be related; however, the myzostomids (tiny ectoparasites on certain echinoderms) are more likely to belong within the annelid phylum (they have annelid-like larvae). Similarly, the acoels are widely believed to have diverged much earlier in animal evolution, even before the divergence of the protostomes and deuterostomes (Ruiz Trillo et al., 1999).

While clearly not the last word, this study represents the state of the art in animal phylogenies; but what of the future? The seminal paper by Field et al. owed much to the development of new techniques for generating data. Twenty years on, the adoption of “next generation” sequencing technologies capable of producing gigabases of data in a few hours may herald the final act in this fascinating field of research. Systematists should not despair of things to do, however. A completely resolved tree of the animal phyla will contain just 30 or so resolved nodes, leaving countless millions of relationships below the level of phyla still to tackle. “This is not the end, nor is it even the beginning of the end, but it is, perhaps, the end of the beginning,” as Winston Churchill might have put it.

REFERENCES


When ATPases Pontin and Reptin Met Telomerase

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Pontin and reptin are conserved AAA+ ATPases identified in chromatin-remodeling complexes. In a recent issue of Cell, Venteicher et al. provide new insight into the function of pontin and reptin in telomerase biogenesis, which is important for cellular senescence, aging, and cancer. These unexpected findings have implications for new avenues for development of effective therapeutic drugs in human disease.

The transcription of most genes is coordinate-ly regulated by transcriptional cofactors and chromatin-remodeling complexes (reviewed by Rosenfeld et al., 2006). Given that chromatin carries DNA and histone modifications to varying degrees and that some of these modifications are associated with transcriptional regulation, chromatin-modifying proteins that modulate epigenetic status are coming into focus. Pontin (also known as Ruvbl1, Rvb1, Tip49, Tip49a, ECP54, NMP238, TAP54α, and pontin52) and reptin (Ruvbl2, Rvb2, Tip48, Tip49b, ECP51, TAP54β, and reptin52) are AAA+ ATPases found in several chromatin-remodeling complexes believed to function in epigenetic regulation (reviewed by Gallant, 2007). From yeast to human, a variety of pontin and reptin-containing complexes have been reported (Figure 1A). Pontin and reptin are components of the INO80 and SWR1 chromatin-remodeling complexes and the Tip60 histone acetyltransferase complex, indicating that pontin and reptin function in the chromatin-remodeling process and transcriptional regulation. Further, pontin and reptin have many binding partners, including transcription factors/coregulators (i.e., c-myc, PROP1, NF-κB p50, TLE, Hint1, and β-catenin) and SUMO modifying enzymes (i.e., UBC9 and SENP1).

Although pontin and reptin are often found together in the same multiprotein complexes, they can act independently or exhibit opposing activities in the regulation of target genes at the mechanistic level. On the metastasis suppressor gene KAI1 promoter, pontin is recruited together with Tip60 as a coactivator complex, whereas reptin and β-catenin function as a transcriptional corepressor complex (Kim et al., 2005). In Wnt/β-catenin signaling pathways, pontin increases the transcriptional activation of Wnt target genes, whereas reptin is a repressor of the β-catenin-TCF4 transactivation complex (Bauer et al., 2000). The pontin/reptin ratio serves to regulate heart growth via the β-catenin pathway in zebrafish embryos, suggesting functional antagonism (Rottbauer et al., 2002). In Drosophila, pontin has been obtained from the Brahma complex and reptin has been isolated from the PRC1 complex, and they regulate Hox gene transcription antagonistically (Diop et al., 2008).

Finally, pontin and reptin met an unexpected partner, telomerase (Venteicher et al., 2008). This finding makes us hold our breath to see what happens next, as the mechanism of upregulation of telomerase and the maintenance of functional telomeres in cancer cells is a highly active research area. Now, we have encountered new players in this interesting game. Telomerase plays a pivotal role in cellular senescence, aging, and cancer and has been focused on as a potential target in anticancer therapy (reviewed by Hahn, 2005; Stewart and Weinberg, 2006). Telomerase is composed of three essential components: the telomerase reverse transcriptase (TERT), the telomerase RNA component (TERC), and the TERC-binding protein dyskerin. Venteicher et al. (2008) performed affinity purification of the TERT complex from HeLa cells and identified the ATPases pontin and reptin as telomerase components. The association of pontin and reptin with TERT occurs at the endogenous level, and reptin is recruited into a TERT complex through bridging pontin.

Given these observations, what are the roles of pontin and reptin in a newly identified telomerase complex? First, pontin and reptin interact with telomerase components TERT and dyskerin and are critical for telomerase activity and for the accumulation of TERC and dyskerin. Second, pontin and reptin form a new TERT-containing complex that is highly S phase specific. The manner in which telomerase is dynamically regulated during the cell cycle has long remained unclear. Venteicher et al. (2008) proposes that S phase-specific interaction between TERT, pontin, and reptin might explain the cell cycle regulation of TERT and the assembly of telomerase in a cell cycle-dependent manner. Further, they suggest that TERT complexes are dynamic and thus that TERT protein exists in at least two different