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Invited Perspectives

Did the ctenophore nervous system evolve independently?

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ABSTRACT

Recent evidence supports the placement of ctenophores as the most distant relative to all other animals. This revised animal tree means that either the ancestor of all animals possessed neurons (and that sponges and placozoans apparently lost them) or that ctenophores developed them independently. Differentiating between these possibilities is important not only from a historical perspective, but also for the interpretation of a wide range of neurobiological results. In this short perspective paper, I review the evidence in support of each scenario and show that the relationship between the nervous system of ctenophores and other animals is an unsolved, yet tractable problem.

The question of how the earliest animals sensed and reacted to their environment has intrigued evolutionary biologists dating back to Darwin (1859). The traditional view of animal evolution is that the earliest ancestors of extant animals lacked neural cell types (Willmer, 1990). Later, a primitive nervous system arose that allowed for more sophisticated interactions with the environment. Recently, phylogenetic analyses of transcriptomic data from many animals (Dunn et al., 2008; Hejnol et al., 2009) and genomic data from the ctenophores *Mnemiopsis leidyi* (Ryan et al., 2013) and *Pleurobrachia bachei* (Moroz et al., 2014) have suggested that ctenophores – rather than sponges – are the most distant relatives to all other animals. This new phylogeny challenges traditional views regarding the timing of important events in animal evolution, including the origin of neurons and the nervous system (Fig. 1).

The ctenophore nervous system is organized as an epithelial nerve net consisting of short "nerve chords" arranged in a polygonal mesh, as well as a less organized mesogleal nerve net made of single neurites (Jager et al., 2011). The apical organ is underlined by its own nerve net (Jager et al., 2011), which includes four putative photoreceptors (Horridge, 1964; Schnitzler et al., 2012). Many ctenophores possess two retractile tentacles, which are innervated by a pair of parallel longitudinal nerve chords (Jager et al., 2011). Ctenophore neurons can be both isopolar and multipolar (Hernandez-Nicaise, 1973); they can also have multiple effectors. For example, giant axons in the lips of *Beröe* make synaptic connections with both muscle fibers and adhesive cells (Tamm and Tamm, 1991).

In the publication of the *M. leidyi* genome, it was proposed that ctenophores *may* have evolved a nervous system independently based on a number of lines of genomic evidence: (i) the absence of some neuronal fate and patterning genes (e.g., Hox), (ii) the absence of some components critical for synaptic function in bilaterians (e.g., neuroligin, CASK, and Erbin), and (iii) the lack of enzymes involved in the biosynthesis of major catecholamine neurotransmitters (e.g., dopamine, norepinephrine, and epinephrine) (Ryan et al., 2013). These results were consistent with earlier focused analyses of the *M. leidyi* genome (Ryan et al., 2010; Liebeskind et al., 2011).

More recently, Moroz and coworkers (2014) have strongly proposed that the ctenophore nervous system *definitively* evolved independently based on similar lines of evidence. Despite the enthusiasm behind the argument for independent origins, there are quite a few lines of evidence uniting the nervous systems of ctenophores, cnidarians, and bilaterians that should be considered. For example: (i) the presence of neuronal fate and patterning genes (e.g., Lhx, Hes, Bhlh, Sox, NKL, and Tlx) (Jager et al., 2006; Derelle and Manuel, 2007; Jager et al., 2008; Layden et al., 2010; Ryan et al., 2010; Simmons et al., 2012; Schnitzler et al., 2014), (ii) the presence of many components critical for synaptic function in bilaterians (e.g., Cadherin, Ephrin, Pmca, mGluR, Magi, Pkc, Citron, Spar, Dlg, Syngap, Gkap, Nos, Lin-7, and Pick1) (Ryan et al., 2013), (iii) observed immunoreactivity to antisera targeted to bilaterian and cnidarian neurotransmitters (e.g., acetylcholinesterase, FMRFamide, and vasopressin) (Hernandez-Nicaise, 1976; Grimmelikhuijzen, 1983; Jager et al., 2011), and (iv) sensitivity to some classical neurotransmitters (e.g., L-glutamate) (Moroz et al., 2014). One can imagine an ancestral nervous system comprised of these shared components that evolved separately in both the ctenophore lineage and the lineage that gave rise to cnidarians

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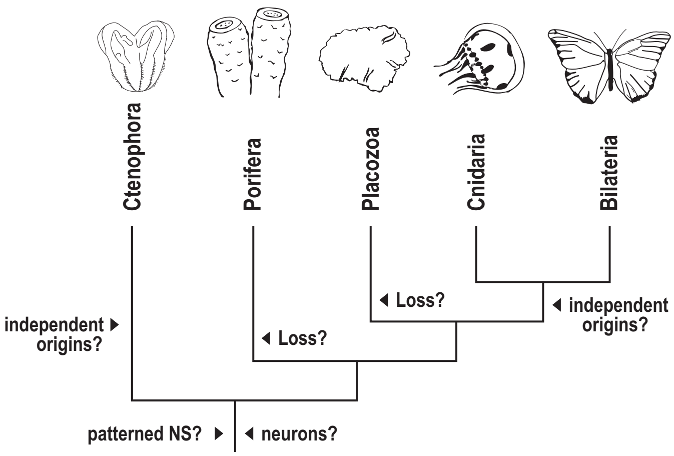

Fig. 1. Phylogenetic relationship of the five main branches of animals based on recent phylogenies (Dunn et al., 2008; Hejnol et al., 2009; Ryan et al., 2013; Moroz et al., 2014). Neurons either originated prior to the last common ancestor of all animals and were subsequently lost in the Porifera and Placozoa lineages, or arose independently at least twice. Likewise, the nervous systems (NS) either arose prior to the last common animal ancestor or separate NS patterning mechanisms arose independently.

and bilaterians. The variety of neurotransmitters used by different types of neurons within the Bilateria contributes to the plausibility of this explanation.

A proper answer to the question of whether the neural cell types in ctenophores, cnidarians, and bilaterians evolved from an ancient ancestor will require functional experiments in ctenophores. For instance, if knockouts of ctenophore genes orthologous to bilaterian synaptic genes lead to phenotypes consistent with synaptic deficiencies, it would seem likely that, from a structural standpoint, neurons descended from a common ancestor. It will also be interesting to determine the extent to which bilaterian neural patterning genes also pattern the nervous system of ctenophores. If any aspect of the ctenophore nervous system can be considered independently evolved, it is perhaps easiest to imagine a completely different set of transcription factors and signaling molecules patterning the nervous systems of ctenophores as compared to cnidarians and bilaterians. However, this proposition would need to be proven with extensive functional assays.

One thing is quite clear: something remarkable happened regarding the evolution of the nervous system very early in animal evolution. Either a nervous system existed in the ancestor and was lost in certain lineages, or ctenophores invented their own nervous system independently (Fig. 1). Either possibility is quite extraordinary. The revelation that ctenophores are the sister group to the rest of animals has sparked a truly exciting debate regarding the evolutionary origins of the nervous system, one that will continue as additional genomic and functional data come to the fore.

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