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Phylogenetic plasticity in the evolution of molluscan neural circuits

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Recent research on molluscan nervous systems provides a unique perspective on the evolution of neural circuits. Molluscs evolved large, encephalized nervous systems independently from other phyla. Homologous body-patterning genes were re-specified in molluscs to create a plethora of body plans and nervous system organizations. Octopuses, having the largest brains of any invertebrate, independently evolved a learning circuit similar in organization and function to the mushroom body of insects and the hippocampus of mammals. In gastropods, homologous neurons have been re-specified for different functions. Even species exhibiting similar, possibly homologous behavior have fundamental differences in the connectivity of the neurons underlying that behavior. Thus, molluscan nervous systems provide clear examples of re-purposing of homologous genes and neurons for neural circuits.

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Introduction

'It is good to have hair-splitters & lumpers.' — Charles Darwin in letter to J.D. Hooker, 1857.

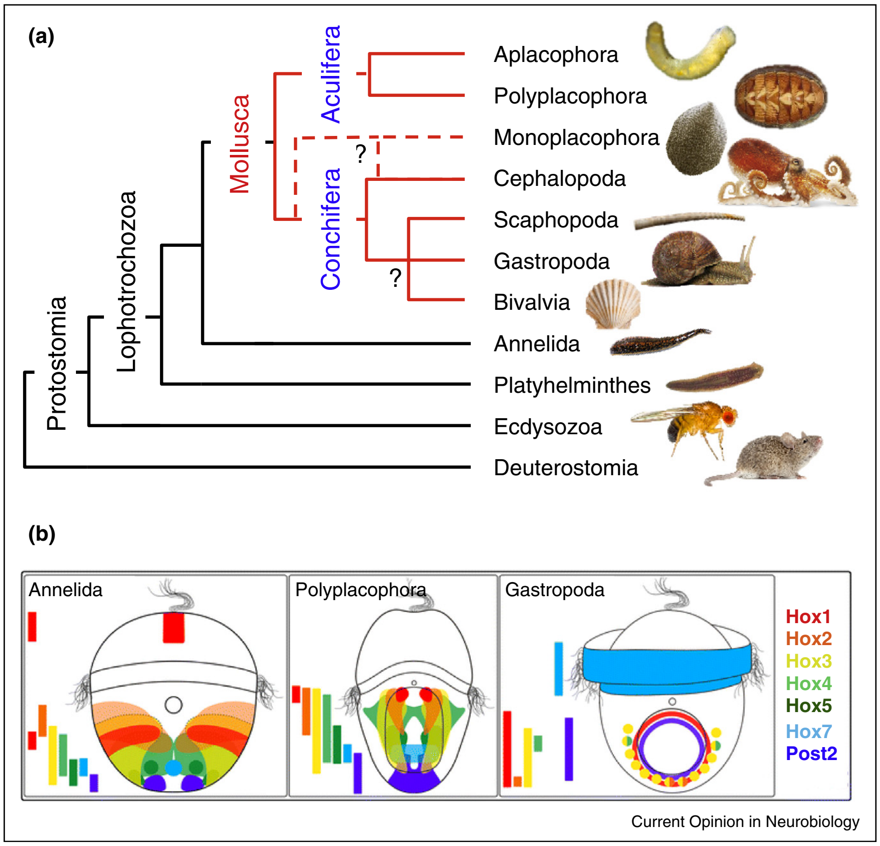
One of the most interesting theories to arise regarding the evolution of nervous systems is that neural centralization occurred in the ancestor of all bilaterian animals and that this common origin is reflected in the organization and patterns of homologous gene expression in the nervous systems of disparate organisms [1–3]. This has led some to speculate that there is deep homology between specific regions and circuits of arthropod, annelid, and vertebrate brains [4,5,6•,7••]. Darwin would have classified as 'lumpers' the people who support the notion that complex nervous systems arose once. There are also 'splitters' who argue that brains evolved several times and co-opted homologous genes [8–10]. The latter argument is based on a cladistic examination of extant nervous systems. These two hypotheses frame a discussion about the role of ancestry and genes in shaping the organization of neural circuits.

Analyses of brain evolution generally have not included molluscan nervous systems. This is a significant omission because molluscs, which include cephalopods, evolved large brains and high intelligence independently from vertebrates. Molluscs also include gastropods, which evolved a highly encephalized nervous system independently from cephalopods. Gastropod nervous systems have been important in neuroscience research because they contain individually identified neurons, allowing specific neural circuitry to be worked out and compared across species. Research on gastropods such as *Aplysia* has led to important discoveries that have implications across phyla [11–13]. Recent research on the evolution and development of molluscan nervous systems and neural circuits is filling this gap. These studies show that genes and neurons have been re-purposed in molluscs. They also show that similar neural networks have evolved independently in cephalopods and vertebrates. Conversely, different neural circuit configurations in gastropods produce similar behavioral outputs.

The molluscan nervous system is not segmented

Molluscs belong to Lophotrochozoa, which includes other major invertebrate phyla such as annelids and platyhelminthes (Figure 1a). Lophotrochozoa is the sister group to Ecdysozoa. Mollusca is a diverse and ancient phylum ranging from worm-like animals, to snails, to octopuses, to clams. There are competing hypotheses regarding the deep phylogeny of molluscs including their position with respect to other lophotrochozoans as well as their split into the sister groups Aculifera and Conchifera (Figure 1a) [14•,15–17]. Although some Aculifera such as chitons (Polyplacaphora) appear to have segmented nervous systems, the apparent segmentation results from ladder-like nerves connecting two axon bundles [18]. Recent evidence from worm-like molluscs indicates that the last common ancestor of the Lophotrochozoa was not segmented; rather, segmentation arose secondarily in annelids [19•]. This is very important because it means that features of the segmented nervous systems in chordates that resemble

Figure 1



Current Opinion in Neurobiology

Phylogeny of mollusca and a comparison of *Hox* gene expression. **(a)** Phylogenetic tree showing the relationship of Mollusca to other major phyla and relationships of major molluscan clades. Many of the ancient relationships are still controversial. Within Mollusca, the tree is based on the phylogenomic work of [16,17,81]. The position of Monoplacophora, in particular, has been debated, as indicated by dashed lines and question mark. Although Scaphopodia, Bivalvia, Gastropoda are in a clade, there is disagreement as to whether Scaphopoda is a sister group to Bivalvia and Gastropoda. **(b)** Comparison of *Hox* gene expression patterns in annelid, polyplacophoran, and gastropod trochophor larvae. Anterior is up in the image. As indicated by the colored bars on the left, there is an anterior–posterior progression of gene expression in the annelid and polyplacophoran larvae, but not in the gastropod where the genes are expressed in specific structures such as the prototroch (blue). The hair-like structures are tufts of cilia. The small circle represents the mouth and the ellipse is the ventral foot.
Source: Modified from Ref. [23•].

those in segmented Lophotrochozoa such as worms are likely due to convergent evolution, not shared ancestry.

Re-specification of morphogenic genes in the development of molluscan nervous systems

Although molluscs are not segmented, some of them have similar gene expression profiles as other bilaterians for antero-posterior patterning genes [20]. For example, in cephalopods, as in most bilaterians, the *Otx* transcription factor gene is expressed anteriorly and is separated from posterior *Hox* expressing regions by *Pax2/5/8* gene expression [21,22••]. However, based on the phylogeny, localization, and timing of expression it seems that *Otx* and *Pax2/5/8* have been recruited for brain area specification in cephalopods independently from flies and mice, representing an example of convergent evolution of gene function [22••].

Molluscs have a complement of up to eleven *Hox* genes and three *ParaHox* genes [23•,24•]. The polyplacophoran mollusc, *Acanthochitona crinita*, exhibits co-linear expression along the antero-posterior axis, not just in the nervous system, but also in ectodermal, endodermal, and mesodermal tissue [23•,24•]. However, gastropods, cephalopods, and probably other conchiferans have secondarily lost this co-linear expression pattern and express *Hox* genes in distinct organs, including portions of the nervous system [25] (Figure 1b). *Hox* genes in cephalopods have complex temporal and spatial expression patterns during development [26•,27]. Several other developmental genes differ in their expression patterns