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Spiralian model systems

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ABSTRACT The "Spiralia" represent one of the three major clades of bilaterian metazoans. Though members of this clade exhibit tremendous diversity in terms of their larval and adult body plans, many share a highly conserved early pattern of development involving a stereotypic cleavage program referred to as spiral cleavage. This group therefore represents an excellent one in which to undertake comparative studies to understand the origins of such diversity from a seemingly common ground plan. These organisms also present varied and diverse modes in terms of their ecology, development and life history strategies. A number of well established and emerging model systems have been developed to undertake studies at the molecular, genetic, cell and organismal levels. The Special Issue of the *Int. J. Dev. Biol.* entitled "Spiralian Model Systems" focuses on these organisms and here, I introduce this clade, pointing out different types of studies being undertaken with representative spiralian model systems.

KEY WORDS: *bilaterian metazoan, spiral cleavage, life history strategy*

The Spiralia (Lophotrochozoa)

Of the three major clades of bilaterians, the Spiralia (Lophotrochozoa) comprise nearly half of the extant metazoan phyla (see Fig. 1). Despite this fact, the group has received relatively little attention compared to the other two clades, the deuterostomes and ecdysozoans, notably in the areas of genetics, as well as molecular, cellular and developmental biology. This is due in part to the long standing predominance of key experimental models positioned within the Ecdysozoa, (e.g., the fruit fly *Drosophila* and the nematode, *C. elegans*), and the Deuterostomia, (e.g., chordates such as the Zebrafish and mouse, as well as a few invertebrate representatives from the Echinodermata).

The Spiralia include 14 of roughly 36 metazoan phyla (Fig. 1). The Spiralia include the Lophotrochozoa, and sometimes these terms have been used synonomously. The clade "Lophotrochozoa" was first recognized by Halanych *et al.,* (1995, see also Giribet *et al*., 2007; Helmkampf *et al*., 2008a,b; Dunn *et al*., 2008; Hejnol *et al*., 2009; Edgecomb *et al*., 2011) who showed that the Lophophorata (consisting of groups possessing characteristic ciliated feeding structures, such as brachiopods and phoronids), are clearly united with other protostome phyla that include annelids, molluscs, and nemerteans. The Spiralia, however, encompass an even larger group of metazoans, and the exact relationships amongst the Spiralia are, however, not fully resolved. The consensus from recent analyses suggest that there are two large sub-groups (clades). One group is the "Trochozoa," (Roule, 1891), which include Annelida, Mollusca, Nemertea, as the "Eutrochozoa", together with the "Brachiozoa" (see Cavalier-Smith, 1998), comprised of Brachiopoda and Phoronida, and the "Polyzoa" (Funch and Kristensen 1995; Passamaneck and Halanych 2006; Helmkampf *et al.,* 2008a,b; Edgecombe *et al.,* 2011) consisting of the Bryozoa, Entoprocta, and Cycliophora. The other group includes the Platyzoa (Cavalier-Smith, 1998; Giribet *et al*., 2000), which include Gastrotricha, Platyhelminthes, and the groups comprising the "Gnathozoa" or "Gnathifera" (Gnathostomulida, Micrognathozoa and Rotifera (Syndermata)). More recently, however, an analysis by Struck *et al.,* (2014), which included additional species, suggests that the Platyzoa are paraphyletic. Their data suggest that, with the exclusion of the Gnathifera, the Gastrotricha and Platyhelminthes comprise a monophylum, which they term the "Rouphozoa." They argue that the Rouphozoa together with the other spiralians comprise a monophyletic group called the "Platytrochozoa." They argue that the Rouphozoa should not be included in the Lophotrochozoa, and that the terms Lophotrochozoa should not be used synonymously with the larger encompassing clade, the Spiralia. Additional lophotrochozoan taxa, with more uncertain affiliations, include the parasitic Acanthocephala (closely related to rotifers), Myzostomida (likely highly derived annelids), and a unique group referred to as the Mesozoa, which includes the Orthinectida and Rhombozoa (see Giribet, 2002, 2008, Hejnol *et al*., 2009; Edgecombe, 2011). These phyla are listed in Table 1 and a recent view of their phylogenetic relationships is depicted in Fig. 1.

The term "Lophotrochozoa" was derived from two of the prin-

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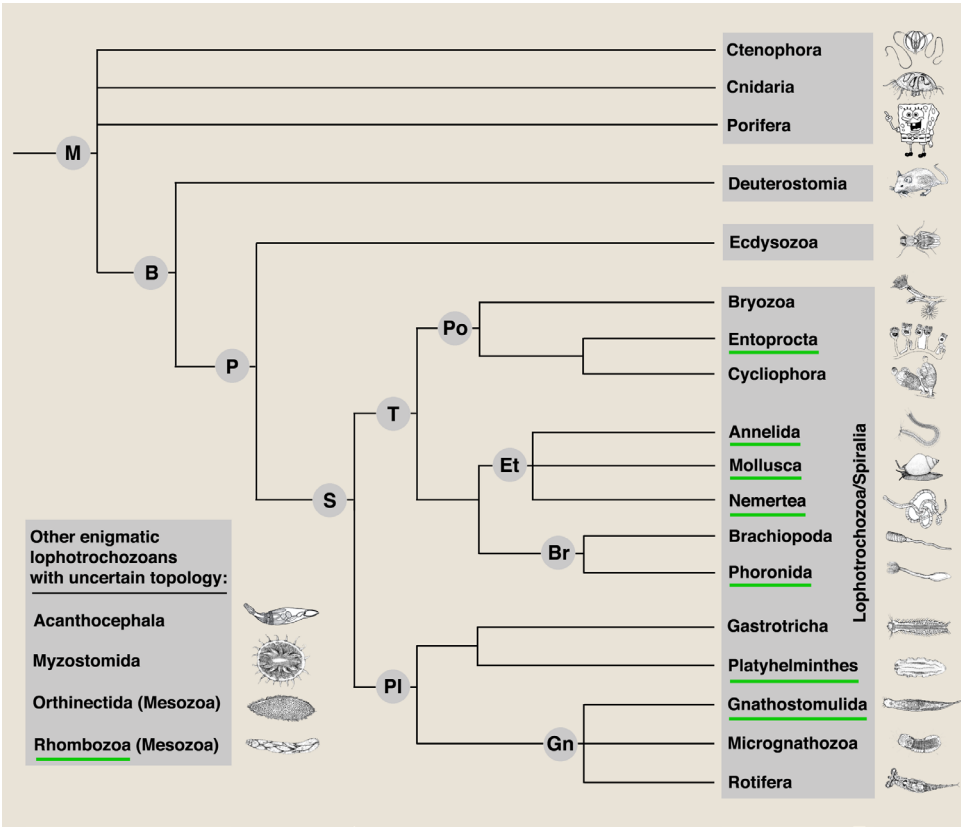

Fig. 1. Phylogenetic relationships between various Lophotrochozoa/Spiralia. *The exact phylogenetic relationships are somewhat unclear. This phylogram is based on a recent consensus reached by several references described in the text. This view does not take into acount the most recent findings of Struck* et al., *(2014), as described in the text, which would remove the Gnathozoa" or "Gnathifera" from the platyzoan clade, and make additional changes to the topology of this tree. Phyla that contain species exhibiting quartet spiral cleavage are underlined in green. Their relationships to the Deuterostomia and Ecdysozoa, as well as a few other basal outgroups are also illustrated. Some enigmatic lophotrochozoans, with uncertain affiliations, are also included in the shaded box to the lower-left. For instance, the Acanthocephala are thought to be related to the Rotifera (Syndermata). The Myzostomida are thought to represent derived annelids. See text for further details. The various named clades are as labeled for particular nodes: M, Metazoa; B, Bilateria; P, Protostomia; S, Spiralia; T, Trochozoa; Pl, Platyzoa; Po, Polyzoa; Et, Eutrochozoa: Br, Brachiozoa; Gn, Gnathozoa.*

ciple morphological characters displayed by different members of this clade. One trait is the ciliated feeding and respiratory tentacles of the *lopho*phore (found in brachiopods and phoronids See Fig. 2L,P) while the other is the ciliated *trocho*phore larva that possesses a prominent ciliated band involved in feeding and locomotion (called the "prototroch" see Fig. 3A), as seen in some annelids and molluscs, and possibly Entoprocts (Nielsen, 2001), nemerteans (Maslakova *et al*., 2004a,b) and Cycliophora (Funch, 1996). However, the underlying synapomorphic trait exhibited by more members of this clade is the highly conserved pattern of early development characterized by a stereotypical cleavage pattern, termed "spiral cleavage" (Fig. 4) At least seven phyla have members that exhibit spiral cleavage including the Annelida, Mollusca, Nemertea, Entoprocta, Gnathostomulida, Platyhelminthes (Polycladida) and dycemid Mesozoa (i.e., Rhombozoa, see Fig. 1, Table 1). Pennerstorfer and Scholtz (2012) also claim that a phoronid (*Phoronis muelleri*) exhibits spiral cleavage (though see Temereva and Malakhov, 2000; and Malakhov and Temereva, 2007). Because of the wider presence of this unifying developmental trait, Giribet (2002, see also Dunn *et al*., 2008, and Hejnol, 2010) argue the lophotrochozoan clade should be referred to as the "Spiralia."

The Spiralia exhibit diverse body plans and life history strategies

Remarkably, the Spiralia have exploited most habitats on earth and exhibit the greatest diversity of body plans compared to any other clade of multicellular organisms (see Fig. 2 and Table 1). In fact, all fundamental grades of organization can be found (Brusca and Brusca, 2003; Ruppert *et al*., 2003). For instance, groups such as the annelids, and molluscs, exhibit mesodermally-lined true coelomic cavities, while others such as the Platyhelminthes, and entoprocts lack these cavities and possess acoelomate or pseudocoelomate body plans. Members of one phyla, the Annelida exhibit overtly segmented bodies along their anterior-posterior axes (Balavoine, 2014; Weisblat and Kuo, 2014, in this issue). Some groups posses skeletal elements such as the external or internal mineralized shells of molluscs and brachiopods or the hardened exoskeletons found amongst the bryozoans. Others possess specialized external or internal cuticular structures, such as those found in entoprocts, annelids, and gnathostomulids, while many representatives have no skeletal elements at all (e.g., nemerteans, phoronids, Platyhelminthes).

Likewise, different groups exhibit varied modes of development, including many with diverse larval body plans (Fig. 3, see papers by Rockman and Zakas, 2014, Arenas-Mena and Li, 2014, Helm *et al*., 2014; Boyle and Rice, 2014, Lesoway *et al*., 2014; Maslakova and Hiebert, 2014, Rockman and Zakas, 2014, all in this issue). As mentioned briefly above, one striking characteristic shared by some members of the annelids and molluscs and possibly also certain nemerteans, bryozoans and cycliophorans is the formation of a trochophore or trochophore-like larvae that possesses a distinct circumferential ciliated band, the prototroch (Fig. 3A,D-E, G). In contrasts, some members of the Nemertea display maximal indirect development via the formation of a feeding larva that contains internal sets of imaginal disks, from which the adult emerges through a radical process of metamorphosis (e.g., heteronemerteans, such as *Cerebratulus lacteus*, or *C. montgomeryi,* Fig. 3F, see review by Maslakova and Hiebert, 2014, in this issue).

Other representatives exhibit direct development without the

TABLE 1

GENERAL CHARACTERISTICS OF VARIOUS SPIRALIAN PHYLA

Taxon	Body Plan Characteristics	Skeletal Elements	Habitats	Modes of Reproduction	Modes of Development	Cleavage Type	Cleavage Asymmetry
(***Polyzoa):***							
Bryozoa	C	Es	M/F/Cl/Ps	Sx/H/As	I	BR	E
Entoprocta	P	C	M/Cl	Sx	I	Sp	E
Cycliophora	A	C	M/Cl/Ps	Sx/As	I	NA	NA
(***Trochozoa):***							
Annelida	C/S	C	M/F/T	Sx/As/(H)	I/D	Sp	E/U
Mollusca	C	Es/Ns	M/F/T/(Ps)	Sx	I/D	Sp/B	E/U
Nemertea	C	-	M/(T)	Sx	I/D	Sp	E
Brachiopoda	C	Es	M	Sx/(H)	I/D	R	E
Phoronida	C	-	M/(Cl)	Sx	I	BR	E
(Platyzoa):							
Gastrotricha	P	C	M/F/T	Sx/H/Pg	D	MR	E
Platyhelmintes	A	-	M/F/T	Sx/H/As	I/D	Sp/Id	E
Gnathostomulida	A	C	M	Sx/H	D	Sp	E
Micrognathozoa	P	C	F	Pg	NA	NA	NA
Rotifera	P	C	F/T/M/(Cl)(Ps)	Sx/As/Pg	D	MR	U
(Other Enigmatic groups):							
Acanthocephala (Rotifera?)	P	-	M/F/T/Ps	Sx	I	MR	U
Myzostomida (Annelida?)	C/S	C	M/Ps	Sx/H	I	Sp	U
Mesozoa (Rhombozoa)	A	-	M/Ps	Sx/As/H	I	Sp	E
Mesozoa (Orthonectida)	A	C	M/Ps	Sx	I	NA	NA

Listing of Lophotrochozoan phyla with details related to which ones exhibit spiral cleavage, different modes of development, larval forms, presence or absence of internal or external skeletal elements, and basic body plan organization.

"Body Plan Characteristics" refers to whether there is a true coelomic cavity (C), or if members of the phylum exhibit a pseudocoelomate (P) or acoelomate condition (A). In addition, groups with an overtly segmented body plan (S) are also indicated. "Skeletal Elements" indicates whether members have cuticles (C) or other cuticluar structures including mouth parts; an endoskelton (Ns, e.g., internal shell); or an exoskeleton (Es, e.g., external shell). (-) indicates skeletal elements are absent. "Modes of Development" refers to whether the embryos develop indirectly (I) via intermediate larval stages or directly (D). "Habitats" refer to whether members of the phylum are found in marine (M), freshwater (F) or terrestrial (T) environments. In many cases terrestrial species are living in water films associated with soil or other substraits or in the case of parasitic forms inside terrestrial hosts. The occurance of parasitism (Ps) is also indicated. The existence of colonial (Cl) organisms is also indicated. "Modes of Reproduction" indicates whether the animals reproduce sexually (Sx), asexually (As) and whether they are hermaphorditic (H) or parthenogenetic (Pg). "Cleavage Type" refers to the presence of spiral (Sp), radial (R), modified radial (MR), bilateral (B), biradial (BR) or idiosyncratic (Id) cleavage patterns. "Cleavage Asymmetry" refers to whether the first few cleavage divisions are symetyric = equal (E) versus asymmetric = unequal (U). (NA) data not available. The presence of these various conditions does not necessarily indicate that these are homologous characters. Designations surrounded by parentheses indicate that relatively few members exhibit these particular conditions (from various sources e.g., Valentine, 1997; Hejnol, 2010; and see text.)

formation of an intervening larval stage (Fig. 3I). Even within the same genus one can find species with dramatically different modes of development. For instance, the genus of calyptraeid snails, *Crepidula* contains at least 60 recognized species (Collin, 2003a,b). Some species, such as *C. fornicata, C. lingulata* and *C. plana* exhibit indirect development with a planktotrophic feeding veliger larvae (Fig. 3D, Conklin, 1897; Werner, 1955; Fretter, 1972; Collin, 2000). On the other hand, species such as *C. adunca,* and *C. convexa* exhibit direct development leading to the formation of crawl-away juvenile snails (Conklin, 1897; Moritz, 1939). Yet others such as *Crepipetella dilatata* (formerly *Crepidula dilatata*) and *Crepidula cf. onyx* form adelphophagic embryos that ingest aborted sibling nurse eggs contained within the same egg capsules (Gallardo, 1977; Chaparro *et al*., 2002; see paper by Lesoway *et al*., 2014 in this issue).

Clearly the spiralian "developmental program" represents a highly flexible platform that supported the explosive radiation of these metazoan phyla. As such, the Spiralia provide an excellent group for studies aimed at understanding the developmental mechanisms that underlie the genesis of such diversity. Obviously, they represent a pivotal group in terms of the emergence of the Bilateria. Though currently lacking, a better understanding of the precise phylogenetic relationships amongst these groups will be critical for deciphering the evolutionary trajectory of those fundamental developmental processes that generated such diverse metazoan adult and larval body plans (see Figs. 2-3). The truly remarkable point is that such vastly different body plans originated from an ancestral pattern of early development that involved spiral cleavage.

Spiral cleavage

The highly stereotyped spiral cleavage pattern exhibited by many members of the Spiralia is characterized by alternating sets of oblique cell divisions that generate staggered quartets of micromeres located towards the animal pole. The basic pattern is illustrated in Fig. 4. Beginning with the fertilized egg, the first two cell divisions occur along the animal-vegetal axis and are nearly orthogonal to one another. These divisions generate four cells ("blastomeres") that establish the four basic embryonic quadrants, which are termed A, B, C, and D following the conventional nomenclature refined by Edwin Grant Conklin (1897, see Figs. 4). In many species symmetric divisions generate these four cells, which are all of roughly the same size (Fig. 4A-D, I). In other species asymmetric divisions generate these cells and typically one cell ends up being larger than the others, the so-called D blastomere (Fig. 4A'-D'). In either case, each of these four cells subsequently generates a series of animal daughter cells (called "micromeres"), which are formed in alternating clockwise and counterclockwise orientations around the animal-vegetal axis (Fig. 4E-H, E'-H', J-M). These animal cells are typically smaller and therefore are termed "micromeres," whereas the four vegetal-most cells are larger and termed "macromeres." In some cases, such as in nemerteans,

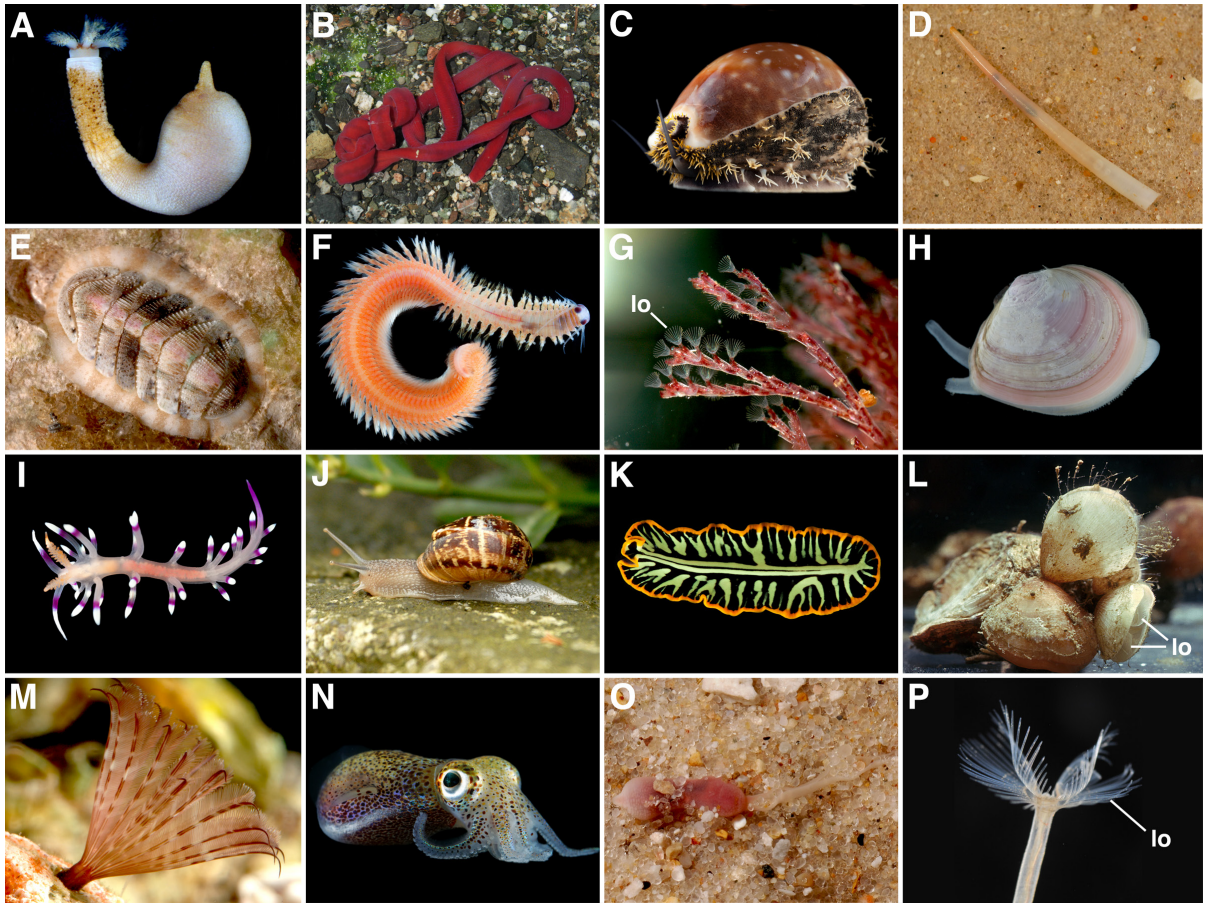

Fig. 2. Representative lophotrochozoans, illustrating some of the tremendous diversity of adult body plans. (A) *The sipunculid,* Themiste alutacea. **(B)** *The nemertean,* Cerebratulus Montgomeryi. **(C)** *A gastropod mollusc, the cowry,* Cypraea vitellus. **(D)** *The mollusc* Dentalium pilsbryi. **(E)** *A polyplacophoran mollusc, the chiton,* Chaetopleura apiculata. **(F)** *The polychaete annelid* Platyneries dumerilii. **(G)** *The bryozoan,* Bugula neritina. **(H)** *The bivalve mollusc,* Macoma balthica. **(I)** *The nudibranch mollusc,* Flabellina exoptata. **(J)** *The terrestrial pulmonate snail,* Helix aspera. **(K)** *The polyclad turbellarian flatworm,* Pseudoceros dimidiatus. **(L)** *The brachiopods,* Terebratulina unquicula. **(M)** *Crown of feeding branciae from an unidentified sabellid "feather duster" annelid worm.* **(N)** *The Hawaiian "bobtail" cephalopod mollusc, the squid,* Euprymna scolopes. **(O)** *The echiurid worm,* Lissomyema mellita. **(P)** *Lophophore of the phoronid,* Phoronis architecta. *Figures were kindly provided by M. Boyle and M. Rice (A), S. Maslakova (B), A. Amiel and E. Röttinger (C, F, H, I, K N), and (D, E, G, J, L, M O, P) are all photos courtesy of M. LaBarbera, ©2013. lo, lophophore.*

the animal micromeres of the first quartet may actually be larger than the macromeres. Animal micromeres are designated with lower case letters, while the vegetal macromeres are designated with uppercase letters. Hence, the first quartet of micromeres is named 1a, 1b, 1c, and 1d, while the corresponding macromeres are named 1A, 1B, 1C, and 1D. (see Fig. 4E-F, E'F', J). While the third cleavage division appears to occur at right angles to those of the first and second divisions the cleavage spindles are actually canted such that the micromeres are usually born with a slight clockwise (dextral) twist relative the macromeres when one views the embryos from the animal pole (see Fig. 4E-F, E'F', J). Subsequently, a second quartet of animal micromeres (2a, 2b, 2c, 2d) is formed by the vegetal macromeres. During this division the spindles become shifted in the opposite direction, such that the second quartet micromeres become situated with a slight counterclockwise twist relative to the four macromeres (2A, 2B, 2C, 2D, Fig. 4G-H, G'H', K). Typically a total of four micromere quartets (collectively referred to as 1q, 2q, 3q, and 4q) are formed and each set is formed with opposing chirality (Fig. 4L-M), though in some species an additional fifth quartet of micromeres may be generated. Of course the individual micromeres belonging to each quartet also undergo further divisions as successive quartets are born and early on these divisions also follow the same alternating oblique orientations. These daughter cells are distinguished from one another by a system of successive superscript numbers (see Conklin, 1897). Typically those daughters born towards the animal pole receive a superscript of 1 while those towards the vegetal pole receive a 2 (e.g., $1b^1$ and $1b^2$, Fig. 34-M), and with successive divisions additional superscripts are added (e.g., $1b^{11}$ and $1b^{12}$).

At some point, the spiral cleavage pattern is interrupted by the occurrence of bilateral sets of cell divisions. Those events represent a key transition in terms of establishing the bilaterian body plan, which is characteristic of both larvae and adults. In most cases the first sign of bilaterality is apparent in the symmetric divisions of cells located in the dorsal D quadrant. For instance, a daughter cell of 1d, $1d^{121}$, which is located at the base of the dorsal arm of the "molluscan cross" divides bilaterally to form cells $1d^{1212}$ (to the right of the midline) and $1d^{1211}$ (to the left of the midline) in the pulmonate

snail *Lymnaea stagnalis*. In many cases 2d also exhibits and early bilaterally symmetric pattern of cell divisions (Dohle, 1999).

In the snail *Crepidula* 4d is the first cell to divide bilaterally to form the ML (left side) and MR (right side) mesendodermal teloblasts well before any of the other fourth quartet micromeres are even born (i.e., 4a, 4b and 4c, see Lyons *et al*., 2012). These teloblasts form bilaterally symmetrical bands of mesendodermal cells (see Lyons *et al*., 2012). These cells also appear to generate the primordial germ cells in all cases in which this has been carefully examined (see reviewed by Rebscher, 2014 in this issue). As development continues, the individual germ layers arise from specific cells and the tissues become organized via the processes of gastrulation (see review by Lyons and Henry, 2014, in this issue), organogenesis and morphogenesis to ultimately generate the larval and/or adult body plans.

It should be noted that there are some species in which alternating micromere quartets are formed with the opposite handedness (i.e., the first quartet micromeres are formed in the counter-clockwise direction, etc.), such as in the snail *Biomphalaria* or even amongst different populations of the same species (e.g., the pond snail *Lymnaea peregra,* Boycott *et al*., 1923, 1930; Sturtevant, 1923; Freeman and Lundelius, 1982; Abe *et al*., 2014, in this issue). Such differences have a profound effect on development, as the early cleavage patterns set up the adult body plan. For instance, in the case of gastropod molluscs such as *Lymnaea*), the chirality of the adult shell (i.e., right- vs. left-handed coiling) is directly related to the chirality of the early cleavage pattern (i.e., whether the first quartet formed via dextral vs. sinistral cleavages, respectively). The mechanisms that underlay the establishment of left-right asymmetry and changes in shell coiling are described further by other authors contributing to this issue (Abe *et al*., 2014; Grande *et al*., 2014, in this issue).

A recent study in annelids (using the leech, *Helobdella austenensis*) suggests that the key transition to bilateral cleavage may be controlled by zygotic gene expression regulated by members of the Pax family of transcription factors, either PaxB1 and/or Pax2/5/8 (Schmerer, *et al*., 2013). This transcription factor appears to be necessary for the DNOPQ''' ectodermal proteloblast (equivalent to 2d[111]) and DM'' mesodermal proteloblast (equivalent to 4d) to undergo their transitions to bilateral cleavage. The fascinating development of the Clitellata, or Oligochaeta, including leeches and the sludge worm, *Tubifex* are described further by Shimizu and Nakamoto (2014, this issue) and Weisblat and Kuo, (2014, this issue). Continued studies of the Spiralia will inform us greatly as to key developmental-evolutionary transitions that have occurred to generate bilaterally symmetrical body plans.

Establishment of the D quadrant

As described above, and depending on the species under consideration, one of two main variations of the spiral cleavage pattern may be observed. In some cases the first two cell divisions are unequal, while in others they are equal. The identity of the D quadrant can be ascertained as soon as the four-cell stage is reached in the former, where the D blastomere is typically much larger then the other cells (Fig. 4A'-D'). On the other hand, the four quadrants cannot be distinguished in the case of the latter (Fig. 4A-D). These differences are closely tied to fundamental differences in the timing and mechanism by which the cell quadrants actually become specified. Multistep models have emerged from

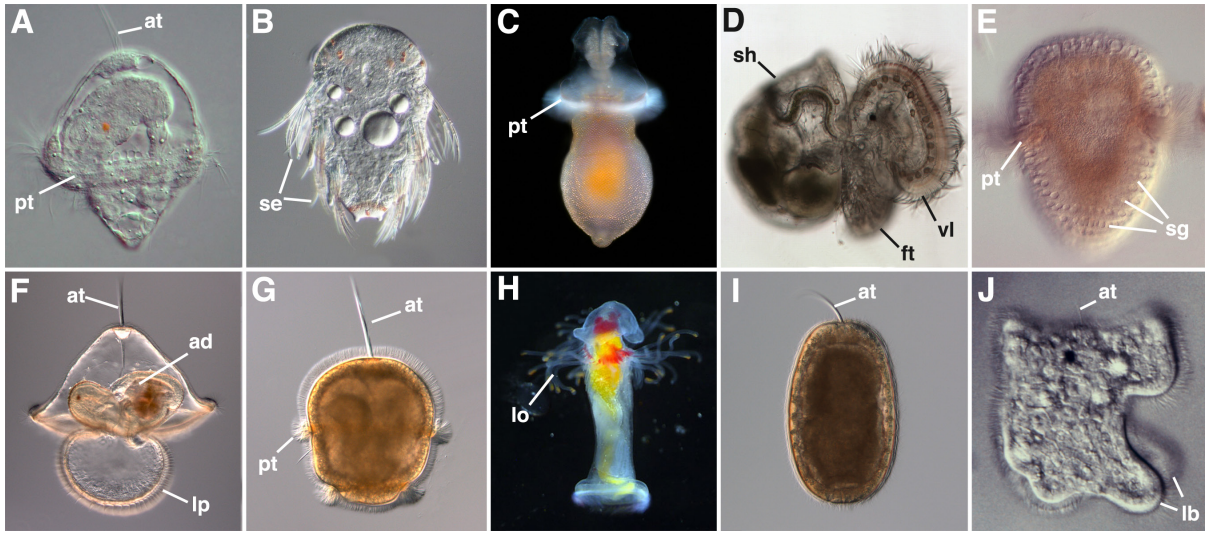

Fig. 3. Representatives lophotrochozoans, illustrating some of the tremendous diversity of larval body plans. *All larvae are shown as dorsal views with the anterior ends toward the top of the figure, except that A and F are left-lateral views and D and J are right-lateral views.* **(A)** *trochophore larva of the polychaete annelid,* Hydroides hexagonus, **(B)** *Setiger larva of the annelid,* Platyneries dumerilii. **(C)** *A sipunculid, "Yellow papillated," pelagosphere larva collected from the Gulf Stream.* **(D)** *Veliger larva of the gastropod mollusc* Crepidula fornicata. **(E)** *Trochophore larvae of the chiton,* Chaetopleura apiculata. **(F)** *Typical, advanced pilidium larva with adult worm seen developing internally from imaginal rudiments (possibly related to* Lineus flavescens). **(G)** *"Trochonemertes" larva of an unidentified nemertean, described as* pilidium nielseni, *and belonging to an undescribed lineiform pilidiophoran species from southern Oregon, otherwise refered to as* Micrura *sp. (see Maslakova and von Dassow, 2012).* **(H)** *Phoronid larval actinotroch collected from Hawaiian waters.* **(I)** *ciliated planula larva of an unidentified nemertean, pilidiophoran species collected near Coos Bay, Or.* **(J)** *Müllers larva of the polyclad trubellarian flatworm,* Hoploplana inquilina. *Some figures were kindly provided by M. Martindale (A, H), N. Rebscher (B), M. Boyle (C), S. Maslakova (F, G, I). ad, adult worm; at, apical tuft; ft, foot; lb, ciliated lobes; lo, lophophore; lp, ciliated lappet; pt, prototroch; sg, shell gland; sh, shell; se, setae; vl, velum.*

experimental data examining these systems that leads to the establishment of the D quadrant and its subsequent activity as an organizer of development (Fig. 5). In the case of species with asymmetric (unequal) cell divisions the larger D quadrant blastomere becomes specified autonomously by virtue of its inheriting specific vegetal determinants (Figs. 4, 5; van den Biggelaar and Guerrier, 1983; Verdonk and Cather, 1983). A specific cell or cells derived from the D quadrant subsequently serve as a key organizer of development to establish the dorso-ventral axis and the fates of adjacent cells (Fig. 5A'-D'; see below). These asymmetric cleavages may take place as a consequence of the asymmetric shifting of the cleavage spindle that dictates where cytokinesis occurs or via the production of vegetal cytoplasmic lobes (so called "polar lobes") that ultimately become shunted into the D quadrant blastomere during each of these divisions (Guerrier *et al.*, 1978; Verdonk and Cather, 1983; Henry and Martindale, 1999). These determinants for the D quadrant are located in the vegetal region, which are also packaged within polar lobes. On the other hand, in those cases that exhibit symmetric (equal) cell divisions, the D quadrant is not specified until later during development and this occurs conditionally by virtue of cell-cell inductive interactions. These inductive interaction take place between daughters of the animal first quartet micromeres (the 1q^{1}s) and one of the vegetal macromeres (e.g., the future 3D), typically early during the interval between fifth and sixth cleavage (Fig. 5A-D). Some data suggests that the distinction between these two forms of spiral cleavage may be closer than had been previously appreciated, as there is evidence that animal-vegetal interactions may also be important for the specification of the D quadrant even in the case of unequal cleavers (e.g., in *Ilyanassa*, Wandelt and Nagy, unpublished data; see Lambert, 2009a,b; Fig. 5B). The nature of these inductive signals is not understood.

The D quadrant organizer

In spiralians, one cell, or in some cases two cells derived from the D quadrant, serve as key embryonic organizers that set up the dorso-ventral axis and direct the development of adjacent cells via inductive interactions (Fig. 5). These cells are set aside relatively early during development. Although these organizer cells reside within the D quadrant, there is a fair degree of heterotopic and heterochronic variation in terms of which particular cell(s) serves

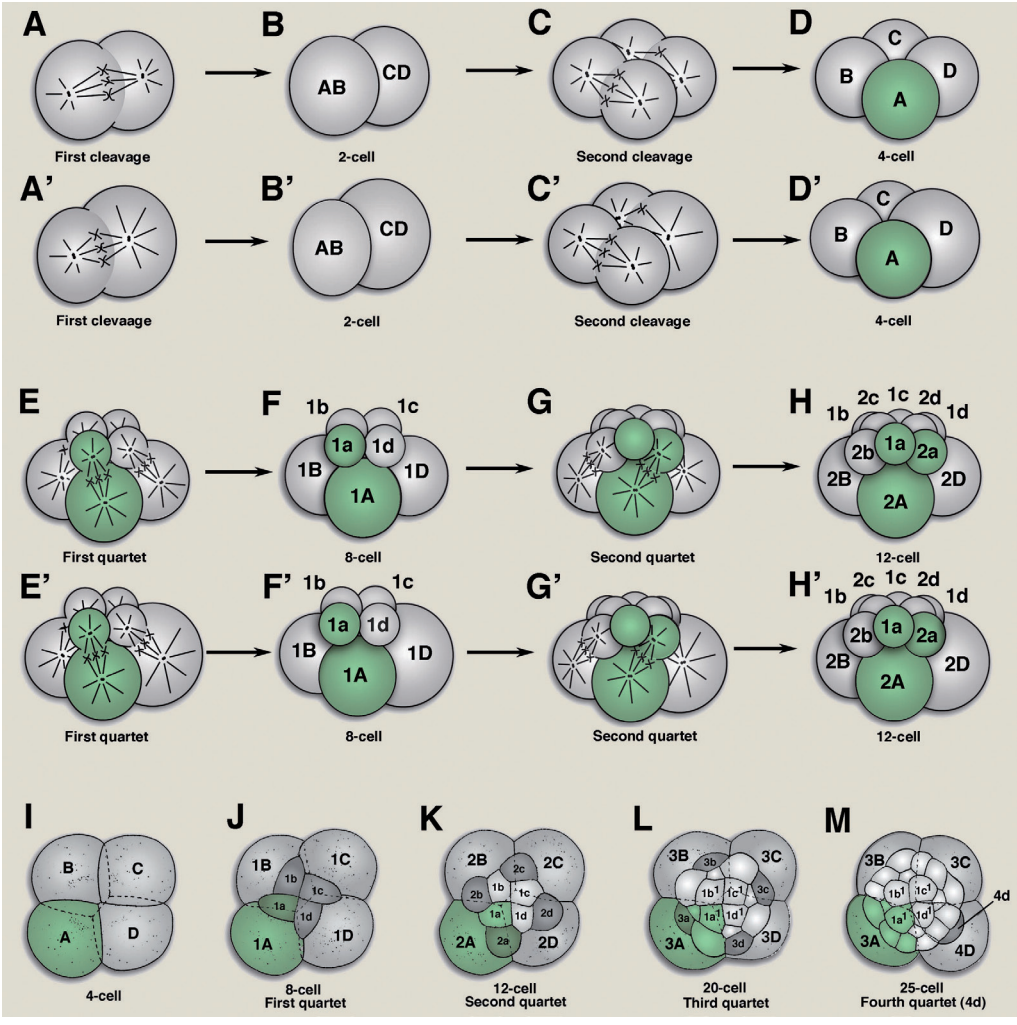

Fig. 4. Diagrams showing equal vs. unequal forms of spiral cleavage. (A-H) *Early cleavage in equal-cleaving embryos illustrating the formation of the first two quartets of micromeres. Note that all blastomeres are of roughly the same size at the two- (A-B) and four-cell stages (C-D), respectively. A'-H'). Early cleavage in unequal-cleaving embryos showing the formation of the first two quartets of micromeres. Note the larger CD and D blastomeres at the two- (A'-B') and four-cell stages (C'-D'), respectively. The embryos in A-H' are shown as lateral views with the animal pole oriented towards the top of the figure and the vegetal pole towards the bottom.* **(I-M)** *Animal pole views of equal cleavage in the mollusc* Crepidula fornicata *(After Henry* et al., *2006, and Conklin, 1897). Cells are labeled following the nomenclature refined by Conklin (1897). In E-H and E'-H' note the alternating oblique orientations of the cleavage spindles that set up the oblique plans of cytokinesis and torted positions of the micromeres. In most species the first quartet micromeres are generated in a clockwise direction relative to the vegetal macromeres as shown in E-F and E'-F' (i.e., "dextral cleavage" se also I-J). The second quartet is generated in a counterclockwise direction (see G-H and G'-H, see also K). Typically, two additional third and fourth quartets of micromeres are formed (see L-M). Note that in some species, such as (*Lymnaea peregra*), the first quartet is formed with the opposite handedness, being generated in a counterclockwise direction ("sinistral cleavage") with each successive quartet also alternating their directions, accordingly (not shown here). See text for further details.*

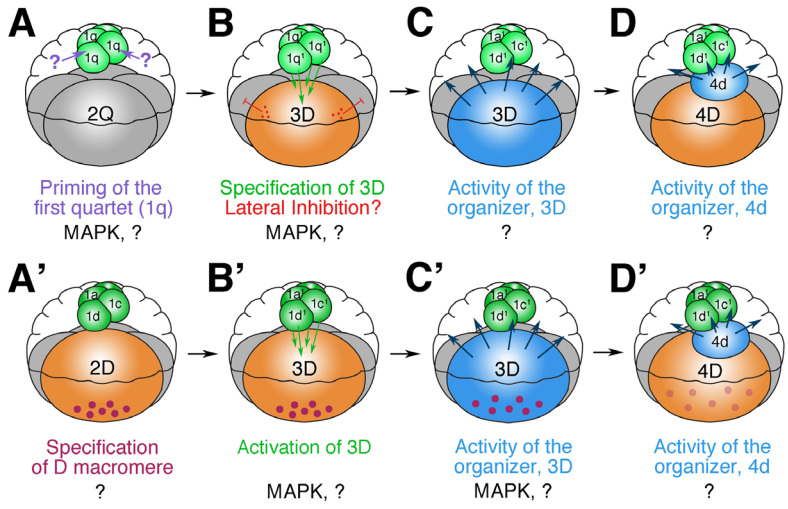

Fig. 5. Models summarizing basic mechanisms involved in specifying the dorsal D quadrant and subsequent D quadrant organizer activity during early developing in spiralians. *A-D highlights these processes in equal-cleaving spiralians. A'-D' illustrates these processes in unequal-cleaving spiralians.* **(A-B)** *In the case of equal-cleaving embryos, the D quadrant is established conditionally, as a result of animal-vegetal inductive interactions that involve the animal-most progeny of the first quartet micromeres (1q^1 cells). Typically this occurs during the interval between fifth and sixth cleavage when animal cells come into contact with one of the four vegetal macromeres and transmit an unknown signal that triggers this cell to become 3D. This series of events appears to trigger MAPK activation within the 3D macromere (Henry and Perry, 2008). On the basis of observations made in one species,* Crepidula*, there may also be an earlier signal that primes the animal micromeres that also involves the activation of MAPK in those cells (Henry and Perry, 2008).* **(B)** *Though all four macromeres are capable of becoming 3D, only one emerges, and this could potentially involve some form of lateral inhibition.* **(C)** *Once the 3D macromere is specified, in some species it becomes a key organizer of developing that sets up the dorso-ventral axis and directs the development of adjacent cells in the other quadrants. The nature of those signals is not clear, though it appears to trigger the activation of MAPK in a subset of animal micromeres.* **(D)** *In some cases 4d may serve as the key organizer (i.e.,* Crepidula*, Henry* et al.*, 2006).* **(A'-B')** *In the case of unequal-cleaving embryos, the D quadrant is established autonomously as a result of the initial asymmetric cell divisions. The first two cell divisions ultimately segregate vegetal determinants (of unknown nature illustrated here as purple dots) into the D blastomere.* **(B')** *Some evidence suggests that the ultimate fate of the 3D macromere may also require inductive interactions from the animal micromeres, similar to the situation encountered in equal-cleaving embryos (Waldelt and Nagy, unpublished data).* **(C')** *Subsequently, the 3D macromere serves as the key organizer of development, in the same fashion described above for equal cleaving embryos.* **(D')** *In the case of* Ilyanassa*, the activity of the organizer appears to be prolonged by 4d. (Lambert, 2009). The fate of the D quadrant, and possibly also its organizer activity also involves the activation of MAPK in these unequal-cleaving species (Lambert and Nagy, 2001, 2003; Koop* et al.*, 2007).*

as the organizer and when this signaling may take place during early development. In the gastropods *Ilyanassa*, and *Lymnaea*, for example, this cell is the macromere 3D, which provides organizer signals during the interval between fifth and sixth cleavage (just before the birth of 4d). In *Ilyanassa*, the activity of 3D is continued somewhat by its daughter 4d (Lambert, 2009a). In *Crepidula* the micromere 4d serves as the principle organizer beginning at the 25-cell stage, prior to the time it divides to form the ML and MR teloblasts, and well before the birth of the other fourth quartet micromeres 4a, 4b, and 4c (Henry *et al*., 2006). In the clitellate annelid *Tubifex*, organizer activity appears to involve two cells, a daughter of 2d, (i.e., 2d^{11}) and 4d, and their signaling takes place at the 22-cell stage (see review by Shimizu and Nakamoto, 2014, in this issue). In another annelid, the polychaete *Capitella teleta*, the organizer is represented by 2d and its signaling occurs at a much earlier stage of development, prior to the birth of the third quartet micromeres (i.e., the 16-cell stage; Amiel *et al*., 2013).

The nature of these inductive signals is not fully understood. However, in some cases MAPK activation (likely as an intermediate in an unidentified signaling cascade) plays a role in establishing the identity of the dorsal D quadrant and possibly in controlling its activity as an organizer (e.g., in *Ilyanassa* and *Crepidula*, Lambert and Nagy, 2001, Koop *et al*., 2007; Henry and Perry, 2008; Lambert, 2009a,b). Application of an inhibitor of MAPK phosphorylation (U0126) leads to radialized forms of development, though in the case of *Crepidula*, MAPK activation is not required specifically in the organizer (4d) itself, but rather for the establishment of the D quadrant macromere 3D or within the animal micromeres that induce this cell to become the D quadrant macromere (Henry and Perry, 2008). On the other hand, activated MAPK does not seem to be important for any of these events in the annelid *Capitella* (Amiel *et al*., 2013). In that species MAPK is first detected in cells located around the blastopore, and MAPK activation does not appear to be critical for normal development. This is in contrast with another annelid, *Hydroides*, where MAPK appears to be activated only in the 4d cell, though the function of MAPK in that system has not been determined (Lambert and Nagy, 2003). We are just beginning to understand the molecular level events that control the processes of cell fate and axis specification during spiralian development (see papers by Gharbiah *et al*., 2014, Pruitt *et al*., 2014, Grande *et al*., 2014, Kenny *et al*., 2014, in this issue).

Cell lineage fate maps

Not only is the cleavage pattern highly conserved, but so to are the general fates of the individual blastomeres. These observations first became apparent from comparative analyses of cell lineages compiled by investigators working at the Marine Biological Laboratory in Woods Hole, MA. The very first of these was carried out by Charles Otis Whitman, who examined development of the leech *Clepsine* (Whitman, 1878, 1887). Leeches, like other oligochaetes, exhibit a modified form of spiral cleavage involving the formation of germinal bandlets that generate most of the adult ectoderm, endoderm and mesoderm (see review by Weisblat and Shankland, 1985; Weisblat and Kuo, 2014 in this issue). In fact, Whitman may be regarded as the "father" of cell lineage analysis. His student Frank Rattray Lillie and other individuals including Edmund Beecher Wilson and Edwin Grant Conklin, subsequently assembled cell lineage fate maps for a number of different spiralians including various annelids *Nereis*, *Arica foetida, Spio fulginosus*, the polyclad *Leptoplana* (Wilson, 1892; Mead, 1897), molluscs, such as the slipper snail *Crepidula fornicata* (Conklin, 1897) the

TABLE 2

COMPARISON OF SEVERAL SPIRALIAN SYSTEMS USED IN VARIOUS STUDIES

Phyla *Genus species*	Cleavage Type (*with polar lobes)	Dev. Mode	Molecular Resources	Viability in Culture^	Regenerative Ability	Ease of Exp. Manipulation	Fate Map	Mol. Funct. Assays	Availibility (# most months)
Mollusca:									
Aplysia california	unequal	I	G, E	higher	+	more challenging	NA	NA	seasonal
Biomphalaria glabrata	equal, sinistral	D	G, E	higher^	NA	more challenging	NA	NA	year round
Bythinia tentaculata	unequal*	I	NA	higher	NA	less challenging	NA	NA	seasonal
Crepidula fornicata	equal*	I	E	higher^	NA	less challenging	+	+	year round#
Dentalium dentale	unequal*	I	NA	higher	NA	less challenging	NA	NA	seasonal
Haliotis asinina	equal	I (NF)	E	higher	NA	less challenging	NA	NA	seasonal
Ilyanassa obsoleta	unequal*	I	E	higher	+	less challenging	+	+	year round#
Loligo pealei	equal, modified	D	E	lower	+	more challenging	NA	NA	seasonal
Lottia gigantea	equal	I (NF)	G, E	lower	NA	more challenging	NA	NA	seasonal
Lymnea spp.	equal, some sinistral	D	NA	higher^	NA	more challenging	+	NA	year round
Patella vulgata	equal	I	NA	higher	NA	less challenging	+	+	seasonal
Spisula solidisima	equal	I	E	higher	NA	more challenging	NA	NA	seasonal
Annelida:									
Capitella teleta	unequal*	I	G, E	higher^	NA	less challenging	+	+	year round
Cheatopterus variopedatus	unequal*	D	E	higher	+	less challenging	NA	NA	seasonal
Enchytraeus coronatus	unequal, modified	D	NA	higher^	+	less challenging	+	NA	year round#
Helobdella robusta	unequal, modified	D	G, E	higher	-	less challenging	+	+	year round
Hirudo medicinalis	unequal, modified	I	NA	lower	-	more challenging	+	-	year round
Hydroides elegans	equal	I	E	higher	+	more challenging	NA	NA	year round
Ophryotrocha labronica	unequal	D	NA	higher^	+	more challenging	NA	NA	year round
Platynereis dumerilii	unequal	I	E	higher^	+	less challenging	+	+*	year round
Pristina leidyi	N.A.	D	E	higher	+	more challenging	NA	NA	year round
Streblospio benedicti	unequal*	I, D	E	higher^	+	NA	NA	NA	year round
Tubifex tubifex	unequal	D	NA	higher^	+	less challenging	+	NA	year round
Nemertea:									
Cerebratulus lacteus	equal	I	E	lower	-	less challenging	+	+	seasonal
Platyhelminthes:									
Dugesia japonica	anarchic, modified	D	E	higher^	+	more challenging	NA	+	year round
Schmidtea mediteranea	anarchic, modified	D	G, E	higher^	+	more challenging	NA	+	year round

Commonly used spiralian model systems compared on the basis of several features, as listed.

"Cleavage Type" indicated is typically spiral with dextral formation of the first quartet of micromeres, unless noted otherwise. Some species exhibit highly modified cleavages that may be non-spiral, such as the cephalopod *L. pealei* and the flatworms *D. japonica* and *S. mediteranea*. Leeches such as *H. robusta* and *H. medicinalis* exhibit a modified from of spiral cleavage. asterix indicates the occurance of vegetal polar lobes during the intital cleavage divisions. "Developmental Mode" referes to either indirect (I, typically with a pelagic larval stage) or direct (D), without an intervening larval phase (NF, referes to the presence of a non-feeding larva). "Molecular Resources" refer to the availability of collections of either genomic (G) and/or EST (E) sequence data, or currently not available (-). "Viability in Culture" refers to whether the systems can be easily maintained long-term in the laboratory. ^Indicates the animals can be reared, egg-to-egg, through successive generations in culture. "Regenerative Ability" refers to whether or not forms of tissue regeneration are known to occur in the adult. "Ease of Exp. Manipulation" refers to whether the embryos are amenible to certain experimental approaches such as microinjection, or alternativley have barriers (such as external investiments, etc.), which make such manipulations more difficult to accomplish. "Fate Map" refers to whether (+) or not (-) there are descriptions of embryonic cleavage and a fate map of these cells. "Mol. Func. Assays" refers to whether or not there have been developed molecular assays to examine gene function (*indicated that transgenic approaches have been developed for this species). Availability refers to the period when embryonic material can be obtained (# means that embryos are available during most months of the year). N.A. data not available. (From various sources, see text).

freshwater bivalve *Unio* (Lillie, 1895). Additional work was carried out by their counterparts in Europe (e.g., Heymons, 1893; Wierzejski, 1905). That early work has been extended in recent decades using modern cell-autonomous lineage tracers for a number of species (i.e., the gastropod molluscs *Crepidula fornicata and C. convexa*, Hejnol *et al.*, 2007; Lyons *et al.*, 2012, and *Ilyanassa obsoleta*, Render 1991, 1997; Chan and Lambert 2014; the polyplacophoran mollusc, *Chaetopleura apiculata,* Henry *et al.*, 2004; the nemerteans, *Cerebratulus lacteus*, Henry and Martindale, 1998, and *Carinoma tremaphoros,* Maslakova *et al.*, 2004a,b; the polyclad turbellarian *Hoploplana inquilina*, Boyer *et al.,* 1996, 1998; and the annelids *Capitella teleta*, Meyer *et al.*, 2010, Meyer and Seaver, 2009, 2010, and *Platynereis dumerilii*, Ackerman *et al.*, 2005; Fischer and Arendt, 2013). Together, this body of work has revealed that the ultimate fates of these quadrants are, to a large extent, homologous across the embryos of different spiralian phyla. Generally speaking, the first three quartets of macromeres give rise to ectodermal tissues, and components of the nervous system, including the photoreceptors (typically derived from 1a[1] and 1c[1]). Specific combinations of cells derived from the second and/or third quartets also generate mesodermal tissues that contribute to the larval and adult body plans (the so-called "ectomesoderm", see review by Lyons and Henry in this issue). The cells of the fourth quartet typically generate endodermal tissues of the digestive tract, though one cell, the mesentoblast 4d, also serves as a mesodermal progenitor (the so-called "endomesoderm"). In many, but not all cases this cell contributes to the formation of the hindgut intestine. The fourth quartet macromeres may or may not form endodermal tissues, depending on the species being examined. As mentioned previously, the D quadrant is the first one to be specified in the embryo and its organizing activity subsequently directs the development of the other cell quadrants.

The positions of the four embryonic quadrants bear a specific relationship to the future dorso-ventral and left-right axes. Some authors have stated that the A, B, C, and D quadrants generally correspond to the right, ventral, left and dorsal sides of the embryo,

respectively, but those relationships are oversimplified. Because individual micromeres within each quadrant are generated with an alternating clockwise/counterclockwise direction, they occupy slightly different positions relative the dorsoventral and left right axes at the completion of these cleavage divisions. Thus, in many cases, the progeny of the first quartet, 1a, 1b, 1c, 1d, occupy left-ventral, right-ventral, right-dorsal and left-dorsal positions, respectively (Henry and Martindale, 1999). The second quartet micromeres occupy left (2a), ventral (2b), right,(2c), and dorsal (2d) positions. The third quartet micromeres exhibit axial relationships similar to those of the first. Finally, the fourth quartet micromeres exhibits axial relationships similar to those of the second. Of course, these are generalities and, in fact, there has been some significant modification of these cleavage patterns and cell fates over the course of metazoan evolutionary history, as described below (see Henry and Martindale, 1999, and the review by Seaver, 2014, in this issue).

Differential localization of mRNAs: specification of the micromere quartets

Elegant work by Lambert and Nagy (2002, see also Kingsley *et al.,* 2007) showed that specific mRNAs are localized to particular cells during early cleavage in the snail *Ilyanassa obsoleta*, and subsequently that some of these mRNAs actually play a role in specifying the fates of the various micromeres (see Swartz *et al*., 2008, Rabinowitz, *et al*., 2008; Rabinowitz and Lambert, 2010; Chan and Lambert, 2011). These mRNAs become shuttled between the cytoplasm, centrosomes and the cell cortex to ultimately become differentially localized to specific daughter cells during cleavage. These localized mRNAs are thought to play key roles in establishing an animal-vegetal pre-pattern that distinguishes the different tiers of micromeres within these embryos (see Lambert, 2009a,b, 2010). Subsequent inductive interactions from the dorsal D quadrant organizer then refine this pattern to impart further complexity within each micromere quartet. Similar patterns of localized mRNAs also appear in the gastropod *Crepidula fornicata* (Henry *et al*., 2010c), and this could be a universal mechanism to distinguish cell fates in the Spiralia.

Evolution of the spiral cleavage program

Although spiral cleavage appears to represent a key aspect of the ancestral mode of development in this group of organisms, it has clearly undergone tremendous modifications, being completely lost in several groups such as the bryozoans, brachiopods and phoronids, in which cleavage appears to be radial. Even within the same phyla there are some representatives that exhibit spiral cleavage such as the polyclad turbellarians, while other platyhelminthes exhibit radically different modes of cleavage (e.g., anarchic cleavage). Another striking example is found in the cephalopod molluscs, which form very large yolky eggs that initially undergo meroblastic bilateral cleavages resembling those seen in avian embryos (Watase, 1888; Arnold, 1965, 1971). Edmund Beecher Wilson (1898) was one of the first to recognize the tremendous degree of conservation between the cleavage patterns and the ultimate fates of identifiable blastomeres in those cases that do undergo spiral cleavage. He referred to these presumed homologies as a form of "ancestral reminiscence." Frank Rattray Lillie (1895, 1899, see Maienschein, 1978) on the other hand noticed interesting differences that led him to understand how specific changes are adaptive to the needs of the organism as it fills a particular niche. For instance, two cells in the embryo of the freshwater clam *Unio* are very large (2d and 2a) and consequently these cells contribute to substantially larger structures in the specialized glocidium larvae (which include the hooked larval valves (shell), and the adductor muscle, respectively). Furthermore, these two cells undergo a more rapid and increased number of cell divisions to form these structures when compared to those of the other embryonic quadrants, 2b and 2c, which are born as much smaller cells. Lillie (1899) referred to these changes as a form of evolutionary "adaptation in cleavage" (see also Seaver, 2014, in this issue).

More recently, Freeman and Lundelius (1992) observed that cleavage involving early equal patterns of cell division is more widely represented in the Spiralia, including the more basal members of this clade (see Tables 1-2 and Figs. 1,4-5). On this basis they argued that this mode of development, which involves epigenetic specification of the D quadrant, represents the ancestral condition amongst this clade. Thus, forms with unequal spiral cleavage are derived, and they argue that unequal cleavage with precocious specification of the D quadrant may permit certain selective advantages that could, for instance, support accelerated development to the larval or juvenile stage. This also implies that embryos that undergo unequal cleavage divisions that involve the formation of polar lobes must have also arisen independently. Though the hypothesis of Freeman and Lundelius (1992) is more widely accepted, Dohle (1999) argued that equal cleavage and late specification of the D quadrant must be a derived condition in the annelids. He based that conclusion on comparisons of the cleavage patterns of the 2d lineage in a number of clitellate and some polychaete annelids, which he argued are too regular.

Spiralian model systems

Over the years, a number of different spiralians have served as models for a variety of studies, and some of these are listed here in Table 2 along with certain features that make these systems so useful. In general, they have been chosen for distinctive advantages that each has to offer, which includes ease of collection/culture, generation time, experimental accessibility (absence of egg investments, ease of microinjection, dissection) ability to examine gene expression/function, access to other resources such as genomic information or EST collections, etc.). Most of these representatives reside within the Mollusca, Annelida and Platyhelminthes, which means there are many gaps in our understanding of the other phyla. More widely used systems for developmental biology include the molluscs, *Lymnaea*, *Ilyanassa* (Gharbiah *et al*., 2009), *Crepidula* (Henry *et al*., 2010a,b), *Patella*, *Dentalium,* and the annelids, *Platynereis* (Fischer *et al*., 2010), *Capitella*, *Hydroides* and leeches such as *Helobdella* and *Hirudo* (Weisblat and Kuo, 2009). The nemertean *Cerebratulus lacteus* has also been used in some developmental studies (Henry and Martindale 1998; Henry, 2002). More recently there has been considerable interest in the evolution of mechanisms that control asymmetry and establishment of the left-right axis. Gastropods snails that exhibit coiled shells have been the subjects of these studies for several years (including, *Lymnaea, Lottia,* and *Biomphalaria*, see papers by Grande *et al*., 2014; Abe *et al*., 2014 and Liu *et al*., 2014, in this issue*)*. Annelids have figured prominently in comparative

studies examining the origins and mechanisms of segmentation (see review by Balavoine, 2014; and Weisblat and Kuo, 2014, in this issue). In fact spiralians have contributed greatly to the recent resurgence of the field of development and evolution and to our understanding of metazoan phylogeny.

The Spiralia contain many systems that are excellent for understanding life history strategies related to transitions between different developmental modes, as well as the process of metamorphosis. As mentioned above, members of the calyoptraeid snails (e.g., species in the genus *Crepidula*) exhibit a tremendous array of developmental modes including forms with direct development and others with planktotrophic feeding larval development or yet others with intermediate forms of development (Henry *et al*., 2010a,b; Lesoway, *et al*., 2014 in this issue). Several species exhibit protandric hermaphroditism, like various *Ophryotrocha* and *Crepidula* species. For instance different members of the genus *Ophryotrocha* exhibit different modes including those with separate sexes (gonochoristic) while others exhibit different forms of hermaphroditism (Åkesson, 1973, 1975, 1994; Paxton and Åkesson, 2010), making them excellent systems for understanding factors that influence sexual development.

Various spiralians exhibit remarkable abilities to undergo asexual reproduction and many can regenerate missing body parts. Numerous studies focusing on regeneration have been carried out using the flatworms *Schmidtea mediterannia* and *Dugesia japonica* (covered extensively in an earlier issue of this journal (*IJDB*, volume 56, 2012). Annelids such as *Ophryotrocha* and *Pristina* can regenerate missing posterior segments and represent excellent systems to study these phenomena (Pfannenstiel, 1974; see articles by Bely, 2014, and Szabó and Ferrier, 2014, in this issue).

Certain systems have been used extensively for studies of neurobiology, such as those with large, easily accessible neurons and relatively simple nervous systems that support complex behaviors, like the squid *Loligo* and *Aplysia (*Abbott *et al.,*1995) and leeches such as *Hirudo* (Muller *et al*., 1981). Several have been used in behavioral studies of learning, memory and behavior, such as *Lymnaea*, (Benjamin and Kemenes, 2009, Feng *et al*., 2009), the limpet, *Lottia gigantea*, (Stimson, 1970, 1973) and the leech (Stent, *et al*., 1984; Muller *et al*., 1981). Annelids such as the leech and the polychaetes *Capitella* and *Platynereis* have also been used to study the development of the nervous system (Stent, 1984; Meyer and Seaver, 2009; see paper by Helm *et al*., 2014 in this issue). Due to the ease with which one can obtain large quantities of gametes, many cell biological, molecular and biochemical studies have been carried out using species such as the surf clam *Spisula*. The oligochaete *Tubifex* (the "sludge worm") and the soil oligochaete *Enchytraeus coronatus* have served as models for studies of toxicology, as well as in developmental biology (see paper by Shimizu and Nakamoto, 2014 in this issue), and serve as important environmental water quality indicator species or in soil toxicity tests, respectively. Studies examining the biology of bio-fouling organisms have examined different organisms such as the calcareous tube dwelling annelid *Hydroides* (Nedved and Hadfield, 2009) and the encrusting bryozoan *Bugula neritina* (Callow and Callow, 2002; Mukaki *et al*., 1997). The Bobtail Squid (*Euprymna scolopes*) has served as a model for understanding the nature of eukaryote-prokaryote mutualism (Lee *et al*., 2009). The freshwater snail *Biomphalaria*, which represents the aquatic host for a key human parasite *Schistosoma* has been studied in order to understand these host-parasite interactions, as a potential means to control this debilitating disease (Morgan *et al*., 2001).

Though the Spiralia currently lack a well established genetic model system, their tremendous strength lies in the rather broad understanding we have of their biology and, as mentioned above, their diverse body plans provide us with excellent subjects in which to undertake comparative studies aimed at understanding the evolution of triplobast bilaterian metazoans. It is only a matter of time before we develop tractable systems in which to undertake genetic analyses and, in fact, some labs are already working towards this end using species, such as the annelids *Streblospio* (see Rockman and Zakas, 2014, in this issue) and *Platynereis* (e.g., lab of Dr. Detlev Arendt, EMBL, Heidelberg, Germany).

The papers featured in this issue highlight many of these tremendous systems and provide examples of the remarkable work that is being carried out by investigators from around the globe. This body of work concentrates mainly on those groups that exhibit the ancestral mode of development that involves spiral cleavage.

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