Selector genes and the Cambrian radiation of Bilateria

(evolutionary constraint/segmentation/homeosis)

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ABSTRACT   There is a significantly greater post-Cambrian decline in frequency of ordinal origination among serially constructed Bilateria, such as arthropods, than in nonserially constructed Bilateria. Greater decline in arthropod ordinal origination is not predicted by ecologic, diversity-dependent models of decline in the production of higher taxa. Reduction in ordinal origination indicates increased constraint on arthropod body-plan evolution. The dispersal of selector genes in the genomes of arthropods in conjunction with the retention of a simple regulatory hierarchy in development may have caused the increased constraint seen. Increased constraint would not be expected in those organisms that are not serially constructed and presumably have not retained the simple ancestral regulatory hierarchy in development of selector gene differentiation of serial elements. The hypothesis of differential constraint tested against the fossil record in this paper can be further tested by examination of the distribution of selector genes in the genomes of arthropods.

Evidence of homology in genes controlling body-plan development suggests a shared ancestry of genetic control of development in highly divergent bilaterian taxa, including insects and vertebrates (1–6). In a phylogenetic context, these shared features of development derive from a common ancestor in the stem of the bilaterian clade and evolved before divergence of the higher metazoan groups we know today. The limited avenues of morphologic evolution permitted by this ancestral form of development may have profoundly affected the evolution of body plans within the Bilateria.

In this paper, homology of genetic control of development in insects and vertebrates is used to characterize the developmental system of the shared ancestor of these Bilateria. The inferred ancestral form of development consists of genes controlling construction of serial elements along the anterior–posterior axis of the body, followed by the differentiation of those serial elements through the activity of an additional set of "selector" genes. This form of development is here termed serial/selector development. Selector genes of the Antennapedia complex of *Drosophila* are used to model the likely limitations and avenues of body-plan evolution permitted by the ancestral serial/selector system of development. Bilateria composed of a simple arrangement of anterior–posterior serial elements, such as annelids and arthropods, experienced a rapid early diversification of body plans; subsequently body-plan evolution among serially organized forms declined. Increased constraint on body-plan evolution in serially organized forms may have resulted from separation in the genome of originally closely linked selector genes. Dispersal of selector genes would have prevented the production of additional body plans generated by the rearrangement of closely linked selector genes. On the other hand, those Bilateria that lack simple serial organization, such as vertebrates and molluscs, probably did not retain the ances-

tral serial/selector form of gene control in development; consequently, the same history of increased constraint in body-plan evolution is not expected in these groups. Evolution of new body plans in these nonserially organized forms did not decrease precipitously.

Ordinal origination of serial forms peaked in the Cambrian period and descended to negligible values in the Post-Paleozoic era. In Bilateria lacking simple serial organization, the peak in ordinal origination occurred in the Ordovician period, and new orders continued to originate in the Post-Paleozoic (Fig. 1). The different histories of serial and nonserial Bilateria predicted and observed here have not been previously recognized. Predictions of morphologic patterns and the distribution of selector genes within organisms can be devised to further test this set of hypotheses.

Homology in Insect and Vertebrate Development

If genes active in the development of divergent taxa are similar in sequence to each other and similar in their pattern of expression during development, then those genes probably derived from an ancestral gene that played a similar role in the development of a common ancestor of the divergent taxa. Among sequence-similar genes expressed in insect and vertebrate development (and other Bilateria examined), genes that also meet the additional criterion of similarity in pattern of expression include those involved in the construction of serial elements, such as the segments in *Drosophila* and the selector genes that differentiate serial elements. Consequently, genes involved in construction of serial elements and selector genes that differentiate serial elements may have played a role in the development of the shared ancestor of insects and vertebrates.

Transcription and translation of a specific set of selector genes in the cells of the individual segments of *Drosophila* is responsible for the construction of the specific morphologic features of the segments composing the *Drosophila* body (7, 8). Several lines of evidence indicate similarity of developmental function and homology between the selector genes of *Drosophila* and sequence-similar selector genes found in vertebrates. Evidence indicating homology include the following: (*i*) the greater similarity in sequences between individual selector genes of insects and vertebrates, rather than among the different selector genes within either *Drosophila* or the mouse (1–5); (*ii*) the identical order of expression along the anterior–posterior axis of *Drosophila* and the mouse of these similar selector genes (2, 3); (*iii*) the identical order of the selector genes themselves in complexes on chromosomes in *Drosophila* and mouse (2, 3); and (*iv*) the similar expression of selector genes within the boundaries of comparable serial elements in insects and the mouse (6).

Given that selector genes in vertebrates and insects are homologous, they must have differentiated the same serial elements in the shared ancestor. There is some evidence suggesting a shared ancestry of genes involved in constructing serial morphogene fields along the anterior–posterior axis of the body in addition to the presence of the selector genes that differentiate them. Among the numerous genes involved

Evolution: Jacobs

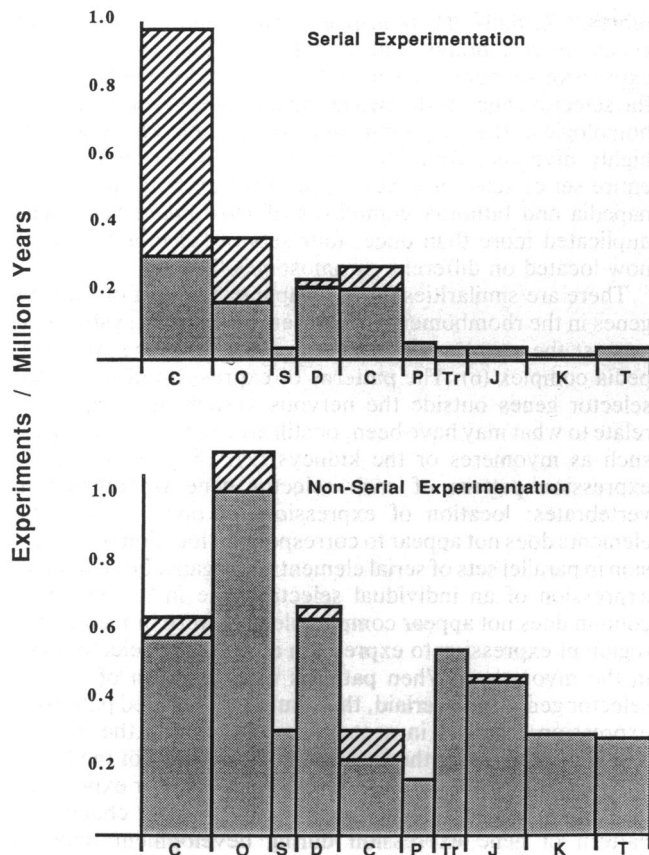*Proc. Natl. Acad. Sci. USA 87 (1990)*   4407

FIG. 1. In these histograms evolutionary novelty or "experiments" in the bilaterian metazoa are quantified for serially constructed and nonserially constructed taxa for each period of Phanerozoic time (39). The experiments are ordinal origination (shaded) and origination of *incertae sedis* of ordinal or higher rank (hatched); these are expressed as a rate (experiments per million yr). Note the rapid production of experiments in the Cambrian period in serially constructed taxa and its rapid decline. Also note that the peak of experimentation is later in nonserially constructed taxa and does not suffer the same decline, continuing to produce new orders in the Mesozoic and Cenozoic eras. C , Cambrian; O, Ordovician; S, Silurian; D, Devonian; C, Carboniferous; P, Permian; Tr, Triassic; J, Jurassic; K, Cretaceous; T, Tertiary.

in segment construction in *Drosophila*, the pattern of expression in the paired and engrailed genes resembles that of sequence-similar genes in other Bilateria. The segment polarity gene engrailed is expressed in the anterior compartment of each segment of *Drosophila* during development. Sequence-similar "engrailed" genes also mark segmental boundaries in several arthropod taxa, including grasshoppers and crayfish (9). The role of the engrailed gene family in nonarthropods is more equivocal. However, genes similar in sequence to engrailed are expressed on serial elements, such as the segments of some oligochaetes during development (10), and the *En* gene of mice is expressed in the anterior portions of each vertebra during its development (11). These observations suggest that an ancestral engrailed gene may have also been involved in construction of serial elements, perhaps in the nervous tissue, of the ancestral bilaterian.*

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*The engrailed gene may not currently perform the same role in segmentation in nonarthropods as it does in arthropods. However, the serial expression of engrailed in some nonarthropods is most parsimoniously explained as a retained ancestral feature. Primacy of selector gene operation in nervous tissue is suggested by the pattern of selector gene expression in vertebrate rhombomeres (6) and the expression of the engrailed segmentation gene in nervous tissue of a number of taxa (10). In flatworms, the sister group of the

Similar arguments pertain to the relationship of the segmentation gene paired of *Drosophila*, which is similar in sequence to the *Pax* gene of mice expressed in intervertebral disks during development (12, 13). This pattern of serial expression probably relates to the construction of serially repeated morphogene fields, suggesting that a form of development in which serial morphogene fields are first constructed and then differentiated by the differential expression of selector genes may have been the ancestral form of development in both insects and vertebrates.

The Phylogenetic Context

Given that insects and vertebrates retain features of the serial/selector form of development, the clade for which serial/selector development is a derived feature must contain both insects and vertebrates. Most phylogenies of the metazoa place the divergence of arthropods (and other protostomes) and the chordates (and other deuterostomes) at a fairly deep branch within the bilaterian metazoa. This placement is borne out by the ribosomal RNA phylogenies of Field *et al.* (14) and Lake (15). These phylogenies indicate that, except for the flatworms, all bilaterian taxa diverged after the bifurcation of a molluscan–annelid–arthropod branch and an echinoderm–chordate branch. Consequently, the serial/selector form of development shared by vertebrates and insects is also a shared feature of all bilaterian taxa (with the possible exception of flatworms). The evidence for expression of selector genes homologous to those of vertebrates and *Drosophila* in the leech (16) and the suggestion of selector gene function indicated by the expression of homeobox-containing genes in discrete serial fields in larval echinoderms (17) confirm that the vertebrate and *Drosophila* examples are not a result of parallel evolution and that the serial/selector form of development was present in the ancestor of the bilaterian clade.

Increasing Constraint in Serial/Selector Development

The best available analogue of a simple hierarchy of seriation followed by selector gene activity is the Antennapedia complex responsible for the differentiation of the cephalar segments of *Drosophila*. In the Antennapedia complex a single selector gene is transcribed in each successive segment (18, 19), and these selector genes appear not to interact with each other. Consequently, regulatory interactions determining cell fate are limited to those interactions required to construct serial morphogene fields and the independent interaction of each selector gene with that set of morphogenes. The limited set of regulatory interactions in this two-step regulatory hierarchy reduces the potential for body-plan evolution resulting from change in gene regulation. The simple regulation of the Antennapedia complex contrasts with the more involved regulation of the bithorax complex of selector genes[†] responsible for differentiation of the thoracic and abdominal segments of *Drosophila*. In the bithorax complex, selector genes regulate each other (20) and an additional hierarchical level of gap genes regulates expression of selector genes in

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rest of the Bilateria, serial features occur in the nervous system, suggesting that selector genes may have first evolved to differentiate elements of the nervous system.

[†]The homeobox regulatory elements of the selector genes of the Antennapedia complex show greater sequence-similarity to one another than do those in the bithorax complex (1). This greater similarity suggests that the selector genes of the Antennapedia complex have been more continuously employed in their developmental roles and are more likely to represent the ancestral form of gene regulation in development than the selector genes in the bithorax complex. Consequently, the Antennapedia complex was chosen as a model for the likely behavior of the ancestral system.

sets of segments (21) rather than just in single segments. These added complexities lead to a larger regulatory nexus. Each regulatory step and regulatory interaction provides additional ways in which cell fate can be manipulated, and consequently provides opportunities for evolutionary modification of the developmental program controlling the body plan.

One means of body-plan change associated with selector gene complexes is homeosis, the expression of a set of morphologic features typical of one position in a series of elements at another position in the series. Homeotic mutations illustrate the different avenues available for body-plan rearrangement depending on different complexities of regulation. In the complexly regulated bithorax complex, homeotic mutations can be brought about by interference with regulatory interaction between selector genes (20, 21). In the simply regulated Antennapedia complex, many homeotic mutations result from inversions (22, 23) that place transcripts under the control of new regulatory elements (the homeobox-containing regulatory elements of nearby selector genes). In a simply regulated set of selector genes, body-plan rearrangement and body-plan evolution may depend on the close linkage of the selector genes.

In a simply regulated selector hierarchy, "hybrid genes" (24, 25) may be of greater importance to body-plan evolution than homeosis. Hybrid genes form when deletion removes the regulatory element of a selector gene. When selector genes are closely linked on a chromosome, deletion of a regulatory region can result in the control by a single selector gene of transcripts previously controlled by different selector genes. This process results not just in a changed position of expression but in the construction of another type of serial element with composite characteristics from the combination of morphologically pertinent information of its transcript. Therefore, hybrid genes may be important for the rapid evolution of novel body plans in the ancestral serial/selector form of development.

If hybrid and/or homeotic gene evolution, dependent on inversion and deletion, are important in body-plan evolution, then dispersal of the selector genes due to introduction of extraneous base-pair sequences or to chromosomal rearrangement is likely to reduce the potential for body-plan evolution as time progesses.‡ As a consequence of their origin by gene duplication (26), the selector genes should have been closely linked on a chromosome in the ancestral condition. However, because of subsequent selector gene dispersal, evolution of the body plan of serially constructed organisms hypothesized to retain the serial/selector form of development is predicted to decrease over time due to breaking up of a region rich in regulatory elements and rich in information pertinent to body-plan evolution.

Lack of Constraint in Organisms Not Composed of Serial Elements

If sets of serially repeated structures arranged along the anterior-posterior axis do not constitute the body plan of a bilaterian, then the simple serial/selector form of development is not likely to be sufficient to construct that body plan. The best understood example of genetic control of development in less serially constructed organisms is that of verte-

brates. Certainly the presence of the same set of selector genes in vertebrates and insects and their similarity of expression demonstrates homology of development between the selector genes of the two groups. However, despite these homologies, the developmental system of vertebrates is highly divergent from that of insects. In vertebrates, the entire set of selector genes represented by both the Antennapedia and bithorax complexes of *Drosophila* have been duplicated more than once; four sets of selector genes are now located on different chromosomes (2, 3).

There are similarities in the simple expression of selector genes in the rhombomeres of the central nervous system that suggest the simple expression of selectors in the Antennapedia complex (6). The patterns of expression of individual selector genes outside the nervous system also appear to relate to what may have been, or still are, elements in a series, such as myomeres or the kidneys (27, 28). However, the expression pattern of each selector gene is complex in vertebrates: location of expression on one set of serial elements does not appear to correspond to location of expression in parallel sets of serial elements or organs. For example, expression of an individual selector gene in the vertebral column does not appear comparable in pattern or identical in region of expression to expression of the same selector gene in the myomeres. When patterns of expression of several selector genes are overlaid, the resulting combined pattern of expression overlaps in a complex way among the various organ systems along the anterior–posterior axis of the body.

In vertebrates the complex patterns of selector expression change as development progresses (29). These changes in pattern of gene expression during development imply a complexity of regulatory interaction determining cell fate over a considerable period in vertebrate development. This temporal complexity of regulatory interaction contrasts with genetic regulation of *Drosophila* development, where selector genes become operative at cell cycle 14 and appear to determine cell fate throughout the body within a single cycle of cell division (30, 31). The complexity of regulatory interaction in vertebrates may preclude some radical body-plan rearrangements, such as homeotic changes involving entire sections of the body. However, the anastomosing web of regulatory interaction in vertebrate development provides a diversity of avenues for reassignment of cell fate and consequently numerous avenues for evolutionary change in body plan.

Vertebrates and, presumably, other organisms no longer composed of a simple set of correlated serial elements probably have not retained the ancestral serial/selector form of development. Consequently, they are not expected to exhibit the same pattern of increased constraint in body-plan evolution expected for those organisms retaining the simple ancestral serial/selector hierarchy of gene regulation in development.

Testing the Predicted Pattern

Given that: (*i*) the serial/selector hierarchy in development is a shared ancestral feature of Bilateria, (*ii*) body-plan evolution in serially constructed organisms may have been increasingly constrained through time, and (*iii*) nonserially organized forms should not be so constrained, the historical pattern of body-plan evolution within the Bilateria can be predicted. This prediction can be tested against the Phanerozoic fossil record of body-plan evolution within the Bilateria. The prediction is simple; there should be a greater decrease in body-plan evolution through the Phanerozoic eon in serially organized forms than in organisms that are not serially constructed. The prediction tested in this paper differs from predictions produced by diversity-dependent

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‡Other explanations for increasing constraint on body plan rearrangement via rearrangement of selector gene expression might include interference from the addition of other levels of gene regulation, such as RNA processing. Such regulation might interfere with the transfer of body-plan building subroutines from one serial element to another. However, the simple dispersal hypothesis proposed here is easily tested by examination of the arrangement of selector genes in the genomes of various organisms.

arguments (32–34) that do not distinguish between serially and nonserially organized taxa.

To examine patterns of body-plan evolutions a metric of evolutionary novelty or experimentation is required. The ordinal level in taxonomy is usually based on discrete differences in body plan; consequently, ordinal origination can be used as a proxy for the frequency of evolution of new body plans (35–37).

In this analysis, ordinal origination, and origination of *incertae sedis* (fossils of uncertain phylogenetic relationship) of ordinal or higher rank are tabulated in two categories, those in groups possessing a serially constructed body plan and those in groups lacking such serial construction. Both categories were tabulated for each geologic period of the Phanerozoic eon (Fig. 1). Information is from Sepkoski's compendium of fossil marine families; no terrestrial taxa are included in the analysis (38). To normalize for period duration, the number of ordinal originations and originations of *incertae sedis* in each period is divided by the duration of the period (39); this metric is termed experimentation per million years.

Experimentation in serially organized forms peaks in the Cambrian period; the peak for nonserial forms is in the subsequent Ordovician period. The declining rate of production of novel body plans results in a hollow curve descending from the Cambrian peak in the serially organized group. Not so for nonserial experimentation; it declines slightly from its Ordovician peak but continues to produce novel body-plans in the Post-Paleozoic era at 15 times the rate of serially constructed forms.

The change in proportion of the serial to nonserial ordinal origination between the Cambrian and Ordovician periods, as well as between the Paleozoic/Post-Paleozoic eras, was tested using a 2 × 2 contingency table analysis. Both χ^2 and Fisher-exact tests indicate a highly significant decline ($P < 0.001$) in the ratio of serial/nonserial ordinal origination between the Cambrian and Ordovician periods and between the Paleozoic and Post-Paleozoic eras. This confirms the significance of the predicted pattern of decline in body-plan evolution in serially organized forms relative to the nonserially organized forms.

Discussion

Taxonomic Basis of the Pattern. The pattern of ordinal origination through time in serially constructed organisms is dominated by arthropods. The pattern of nonserial ordinal origination is made up of a balance of several phyla. Although dominated by arthropods, the pattern of origination of serially constructed orders is not a consequence of any single class; the trilobites, crustaceans, and chelicerates all contribute to the Cambrian peak in ordinal origination. Taxa of unknown class-level affinity also contribute greatly to the radiation of serially constructed arthropodous forms in the Cambrian period. The uncertain affinities of these demonstrably arthropodous forms is consistent with the radical body-plan rearrangement expected of homeotic or hybrid gene evolution. The Ordovician radiation of nonserial forms includes a balance of echinoderm and molluscan orders, as well as bryozoans and brachiopods; the Post-Paleozoic nonserial originations include large numbers of echinoderm and vertebrate, as well as molluscan orders.

Constraint in Arthropods. The decline in production of new orders of serially constructed taxa results primarily from a decline in production of new arthropod orders. The similarity of "engrailed" gene expression in segment construction in diverse arthropod taxa (9) and the comprehensively segmented body plan in arthropods suggest that a serial/selector form of development may be similarly used in all arthropods. These observations support the interpretation that increased

constraint on the evolution of arthropod body plans may result from changing properties of the serial/selector regulatory gene hierarchy that controls body-plan development.

Origination of Higher Taxa. The decline in origination of higher taxa from a Cambrian peak has often been explained as a consequence of negative feedback as diversity increases (32–34) and niches fill. The greater decline in body-plan evolution in serially constructed forms as opposed to those lacking serial construction is not a prediction of simple models of diversity dependence. Consequently, diversity-dependent explanations are not sufficient to explain the pattern of differential decline in origination.

Additional Predictions. The hypothesis that serial/selector development is ancestral in the bilaterian clade and that the serial/selector form of development may exert a controlling influence on body-plan evolution in arthropods has broad implications. Many of these implications can be viewed in the context of predictions that can be used to further test and modify these hypotheses. These predictions involve patterns of body-plan organization in and among ancient and modern taxa and patterns of selector gene organization within modern Bilateria.

Predictions involving body-plan organization include the following: (*i*) If ancestral bilaterians were serially constructed with one or a few differentiated elements, the late Precambrian (Vendian) fossil record should contain evidence of these forms. Vendian forms that merit further investigation would include those composed of serial elements with a differentiated anterior element, such as *Spriggina, Vendia,* and *Vendomia*. However, the affinities of these Vendian taxa with the metazoa and the nature of their body-plan construction is controversial (40, 41). (*ii*) In Bilateria currently lacking a serial body plan there should be some evidence of a serially constructed ancestor, and this is the case in a number of major bilaterian taxa. Most modern molluscs lack well developed serial features; however, the serial features of Monoplacophora and Polyplacophora and the sister group relationship of segmented arthropods and annelids to molluscs (14, 15) suggest that molluscs may have serially constructed ancestors. A number of phyla that are not simply constructed of serial elements today retain a trimerous larval condition, suggesting a serial ancestry. These taxa include brachiopods, echinoderms, and other deuterostome phyla (42). The likelihood that serial construction is ancestral can be used to determine the polarity of characters important in phylogenetic analyses. Consistency of the resultant taxonomies could then be viewed as a test for the serial-ancestry prediction. (*iii*) If homeotic or hybrid gene evolution were important in the evolution of body plans in arthropod groups, then differences attributable to these evolutionary mechanisms should be discernable between taxa involved in the radiation of arthropod clades. The ordinal level within the malacostracan crustaceans (43) and the generic level within Upper Cambrian trilobites (F. Sundberg, personal communication) appear promising for this kind of analysis. Taxonomic differences in these groups are often distinguished by shifts of segmental features of potential homeotic or hybrid gene origin.

A prediction that involves gene organization as well as morphology can be derived from arthropod living fossils, such as *Limulus,* remipedes, Onychophora, scorpions, whipscorpions, and spiders. These arthropod body plans have been stable for hundreds of millions of years. This stability could be due to the loss of potential for body-plan evolution due to dispersal of selector genes in the genome. This prediction can be tested by comparison of the distribution of selector genes in the genomes of arthropods with varying durations of body-plan stability; those that have undergone more recent body-plan evolution, such as the malacostracans or, possibly, insects might be expected to have more closely

linked selector genes than those that have not recently undergone such evolution.

Conclusions

Ordinal origination in serially constructed forms decreases more dramatically from a Cambrian peak than ordinal origination in nonserially constructed forms. Therefore, a simple diversity-dependent model is not a sufficient or complete explanation for the decline in the production of higher taxa since the Cambrian period.

Decline in production of ordinal origination among serially constructed forms results from a decline in the production of new arthropod body plans. This reduced body-plan evolution may be the consequence of dispersal of selector genes in the genomes of arthropods that also retain a serial/selector hierarchy in development. Nonserially constructed phyla probably do not retain this ancestral simple regulatory hierarchy and do not suffer this same reduction in rate of production of new body plans; additional orders continue to be produced into the Post-Paleozoic era.

The hypothesis that the serial/selector form of development evolved in the stem group of the Bilateria and constrained the history of body-plan evolution in arthropods generates a range of morphologic and genetic predictions to further test and modify the hypothesis.

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