

Homology and the hierarchy of biological systems

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Summary

Homology is the similarity between organisms due to common ancestry. Introduced by Richard Owen in 1843 in a paper entitled “Lectures on comparative anatomy and physiology of the invertebrate animals”, the concept of homology predates Darwin’s “Origin of Species” and has been very influential throughout the history of evolutionary biology. Although homology is the central concept of all comparative biology and provides a logical basis for it, the definition of the term and the criteria of its application remain controversial. Here, I will discuss homology in the context of the hierarchy of biological organization. I will provide insights gained from an exemplary case study in evolutionary developmental biology that indicates the uncoupling of homology at different levels of biological organization. I argue that continuity and hierarchy are separate but equally important issues of homology. *BioEssays* 30:653–658, 2008. © 2008 Wiley Periodicals, Inc.

Introduction

“Homologue...The same organ in different animals under every variety of form and function.” Owen, 1843, pp. 379.⁽¹⁾

Ever since Darwin, the concept of homology has been a central part of evolutionary and comparative biology. While there is general agreement on the importance of the homology concept, its exact definition and many of its applications are still highly controversial. Numerous excellent books and reviews have been written about theoretical and descriptive issues on homology, so that I will skip a general introduction and refer the interested reader to recent publications.^(2–5) Instead, I will focus on an example from evolutionary developmental biology that illustrates the uncoupling of homology at different levels of biological organization, an aspect that is often neglected among evolutionary biologists.

From continuity to hierarchy

The concept of homology was originally applied in comparative morphology and anatomy. In the Darwinian view, homology is the continuity of descent: similar characters and also dissimilar

characters, when connected through intermediate forms, have homology relationships because the genetic information generating these structures is continuous. In this context, the analysis of homologous relationships was restricted to such inter-species approaches, which compared (the same) structures among extant or fossil species. In modern biology, genetic and molecular tools provide mechanistic insight into the development of structural modules. The genetic and molecular understanding of development allows the inter-species view of homology to be extended to a hierarchical intra-species perspective. In evolutionary developmental biology, such a hierarchical intra-species perspective can be combined with inter-species and inter-taxic comparisons.^(6,7) The key question behind this idea is whether the genetic information that generates homologous structural entities is necessarily itself homologous: are homologous organs, tissues and cells, specified by homologous genes, signaling pathways and gene regulatory networks?

Homology and hierarchy: the uncoupling of homology at different levels of biological organization

Here, I argue that there is a potential uncoupling of homology at different hierarchical levels of biological organization. This uncoupling can go both ways: non-homologous genes might control the formation of the same (homologous) organ in different species and homologous genes might serve independent functions in different organisms. The idea that different networks can control the formation of the same organ dates back to de Beer.⁽⁸⁾ More recently, several publications have arrived at similar conclusions,^(4,6,7) but many discussions about homology still disregard the hierarchical perspective of homology. In the following, I will provide an example from evolutionary developmental biology to indicate how the molecular mechanisms of patterning processes and the final morphological trait that is generated by these processes can be uncoupled. It is important to emphasize that the presentation of just one case study as given below does not mean that there are no other examples. Rather, this restriction was deliberately chosen to lend sufficient depth to the present description.

Patterning and induction of the *C. elegans* vulva

The free-living nematode *Caenorhabditis elegans* with its fixed cell lineage provides a unique object for analyzing the postembryonic development of morphological structures with

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single cell resolution.⁽⁹⁾ Similarly, the cell lineage of other nematode species can be studied with the same precision.⁽⁷⁾ Therefore, developmental and evolutionary studies in nematodes allow an intra-species approach to homology by comparing structural entities at a continuum of hierarchical levels: morphology, cells, molecular signaling pathway and individual genes.

Of the many developmental processes that have been extensively studied in *C. elegans*, the development of the vulva, the egg-laying structure of the hermaphrodite, is a prominent example. By origin, the vulva is a derivative of the ventral epidermis. Three of the 12 ventral epidermal precursor cells form the entire structure after generating 22 progeny (Fig. 1A,B). During vulva formation, many of the known concepts of development are involved: First, positional information provided by the Hox gene *lin-39* restricts the developmental competence to form vulval tissue to six of the 12 epidermal cells, namely to those located in the central body region.^(10,11) Second, induction by an organizer, the gonadal anchor cell (AC), which is located dorsally of the future vulva, initiates vulva differentiation in three of the six potential vulva precursor cells (VPCs) (Fig. 1B).⁽¹²⁾ This well-studied induction event involves the EGF–RAS signaling pathway, making *C. elegans* vulva formation a platform for the analysis of oncogenetic processes.⁽¹³⁾ Third, several additional cell–cell interactions guarantee precise vulva patterning, involving Wnt and LIN-12–Notch signaling as well as complex chromatin remodeling mechanisms.^(14,15) One key aspect of the molecular processes regulating vulva formation is redundancy, the fact that several molecular pathways act in parallel to provide robust developmental patterning.

At the end of larval development, the 12 ventral epidermal cells, which are named P1.p to P12.p from anterior to posterior, have adopted one of four alternative cell fates in a stereotypical manner: Non-vulval cells in the anterior and posterior body region, P1.p, P2.p, P9.p–P11.p, which have not been specified by the Hox gene *lin-39*, fuse with the surrounding hypodermis in the first larval stage (Fig. 1A,B). In the central body region, those three cells that were specified by LIN-39 but were not induced by the EGF signal divide once in the third larval stage and then also fuse with the surrounding hypodermis. The fate of these cells, P3.p, P4.p and P8.p, is designated as 3° cells. The three central cells, which are induced by the AC signal adopt one of two alternative fates: P5.p and P7.p adopt the 2° fate and form the outer part of the vulva, whereas P6.p adopts the 1° fate and forms the inner part. Finally, one important aspect of vulva formation is that all of the six VPCs, P3.p–P8.p, have the competence to participate in vulva formation. If any or all of the central cells P5.p–P7.p are ablated by laser microbeam irradiation, P3.p, P4.p and P8.p can replace these cells so that a normal vulva is formed. Thus, P3.p–P8.p form a so-called vulva equivalence group (VEG). Thirty years after the description of the cell lineage of *C. elegans*,⁽⁹⁾ we have a thorough understanding of the cellular, genetic and molecular processes involved in vulva formation. This is the starting point from where to set out to investigate the evolution of vulva formation and consider the homology concept.

Vulva evolution: a homologous organ from homologous precursor cells

The detailed understanding of *C. elegans* vulva formation provides a paradigm for studying the evolution of this

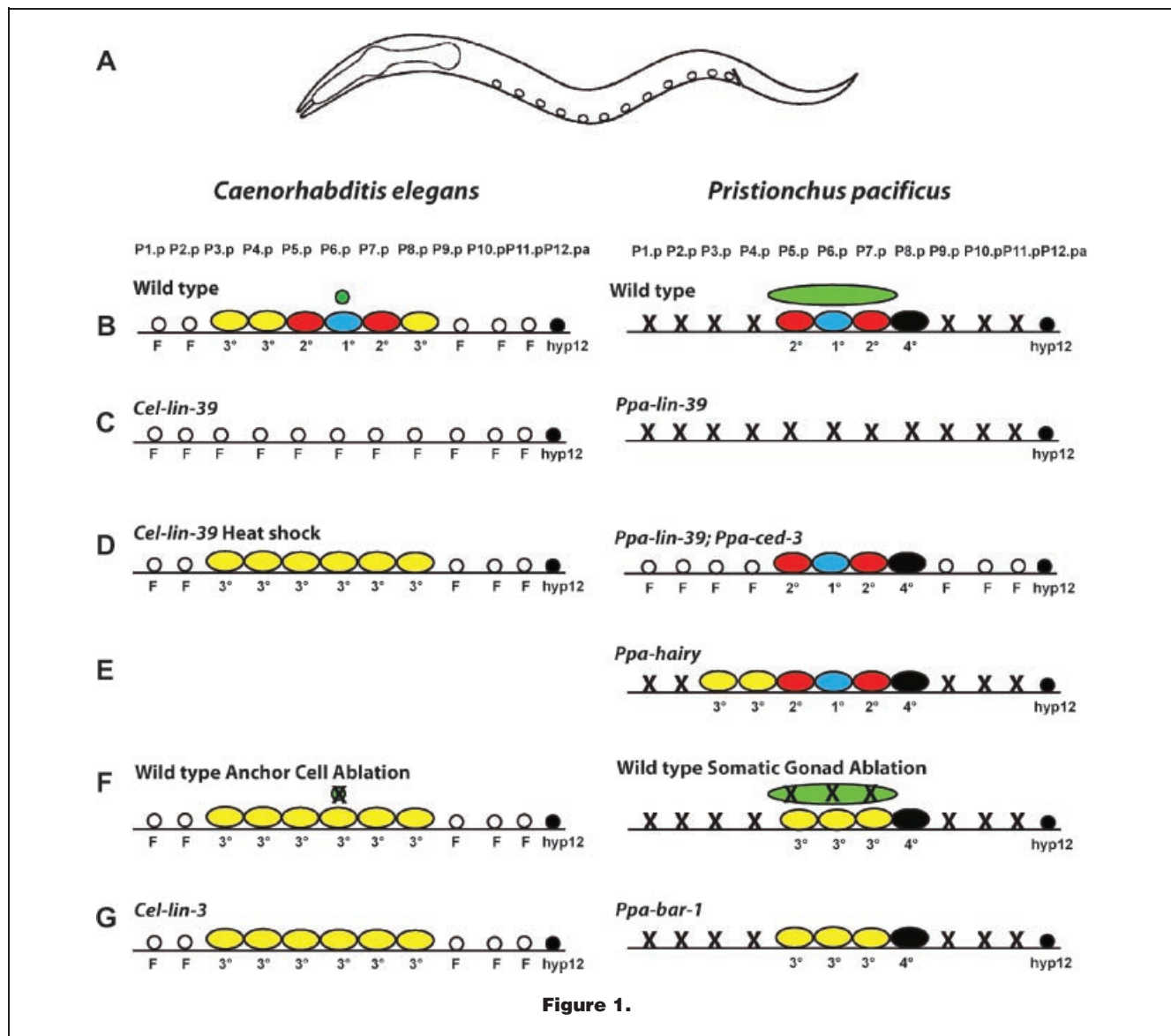
Figure 1. Schematic summary of ventral epidermal cell fate specification in *P. pacificus* and *C. elegans* wild-type and mutant animals. **A:** The ventral epidermis of hermaphrodites derives from 12 ectoblasts, named P1.p–P12.p according to their anteroposterior position. The 12 cells are equally distributed between pharynx and rectum. **B:** Wild-type animals. In *C. elegans*, the vulva is formed from the progeny of P5.p–P7.p. P6.p has the 1° fate and generates eight progeny (blue ovals) and P5 and P7.p have the 2° fate and form seven progeny each (red ovals). P3.p, P4.p and P8.p have the 3° fate (yellow ovals). These cells are competent to form vulval tissue, but remain epidermal under wild-type conditions. P1.p, P2.p, P9.p–P11.p fuse (white circles) with the hypodermis and are not competent to form part of the vulva. P12.p is a special cell called *hyp12* and forms part of the rectum. In *P. pacificus*, P1.p–P4.p, and P9.p–P11.p die of programmed cell death (X) and reduce the size of the vulva equivalence group further. P5.p–P7.p have a 2°–1°–2° pattern, such as in *C. elegans* and P8.p is a special epidermal cell (black oval), which is designated as 4° cell fate. **C:** *lin-39* mutants. In *Cel-lin-39* mutants, positional information for the formation of the vulva equivalence group is missing and P3.p–P8.p fuse with the hypodermis, like their lineage counterparts in the anterior and posterior body region. In *Ppa-lin-39* mutants, the vulva equivalence group is not formed and P5.p–P8.p die of programmed cell death. **D:** In *Cel-lin-39* mutants, in which a *Cel-lin-39* transgene is under the control of a heat-shock promoter, heat-shock treatment in late embryogenesis can rescue the early phenotype of *Cel-lin-39* described in C. In such animals, the absence of *Cel-lin-39* activity during vulva induction results in a vulvaless phenotype and P5.p–P7.p have a 3° cell fate. In *Ppa-lin-39* mutants, the cell death phenotype of Pn.p cells can be rescued by depleting *Ppa-ced-3* function, a gene that is necessary for the execution of programmed cell death. *Ppa-lin-39*; *Ppa-ced-3* double mutants form a normal vulva, indicating that *Ppa-lin-39* is dispensable for vulva induction. **E:** *Ppa-hairy* is involved in regulating the size of the vulva equivalence group. In *Ppa-hairy* mutants, P3.p and P4.p survive and form a vulva equivalence group that is reminiscent to the pattern in *C. elegans* wild-type animals. There is no 1:1 ortholog of *Ppa-hairy* in the *C. elegans* genome. **F:** AC and somatic gonad ablation in wild-type animals. In *C. elegans*, ablation of the AC at birth is sufficient to prevent vulva induction. In *P. pacificus*, multiple cells of the somatic gonad are involved in vulva induction. The later that these cells are ablated in development, the more vulva differentiation is seen in ablated animals. Only the ablation of the somatic gonad at hatching, results in the complete absence of vulva differentiation. **G:** Mutations resulting in complete vulvaless phenotypes. In *C. elegans*, mutations in the EGF family member *lin-3* result in a vulvaless phenotype. In *P. pacificus*, mutations in the β -catenin like gene *Ppa-bar-1* completely phenocopy gonad-ablated animals.

developmental process. For more than 10 years now, several laboratories have been studying various aspects of vulva formation in more than 50 different nematode species belonging to several distinct families.^(16,17) All known nematodes have a vulva and nematologists have always assumed that the vulva is a homologous organ. But what about the cellular basis of vulva formation? Comparative cell lineage analysis has revealed that the vulva is indeed formed from homologous precursor cells in all studied species. Specifically, the vulva derives from P5.p–P7.p or P5.p–P8.p with a 2°-1°-2° or 2°-1°-1°-2° pattern, respectively, which is identical or very similar to what is known from *C. elegans*. Even species that form their vulva in the posterior body region rely on P5.p–P7.p, which are born in the central body region, as in *C. elegans*, and then migrate towards the posterior where they initiate vulva

differentiation.⁽¹⁸⁾ Therefore, comparative cell lineage analysis clearly indicates that the vulva is a homologous organ made by homologous precursor cells. Finally, it should be emphasized that this important finding was facilitated by the fact that the 12 ventral epidermal blast cells can easily be homologized in the hatching larvae of all studied nematodes based on form, position and their asymmetric cell divisions during the first larval stage.

Cell-cell interactions during vulva formation are species-specific

Initial insight into the functional aspects of nematode vulva formation was provided by cell ablation studies and important differences between species became apparent immediately.



Surprisingly, the strongest functional differences were observed with respect to vulva induction. While *C. elegans* vulva formation relies on a 1-step induction by the AC,⁽¹²⁾ comparative studies revealed the presence of a two or even three step induction in other nematodes.⁽¹⁹⁾ In species with a posterior vulva, the VPCs do not rely on inductive input by the somatic gonad, but show autonomous specification properties.⁽¹⁸⁾ More recent work indicated that the exact mechanisms of vulva induction vary even within the genus *Caenorhabditis*.⁽²⁰⁾ Thus, the formation of a homologous organ by homologous precursor cells relies on species-specific cell–cell interactions raising the question about the underlying genetic and molecular principles.

A two-species comparison: *Pristionchus pacificus* as a partner for *C. elegans*

The elucidation of the molecular mechanisms of developmental processes requires multiple genetic, genomic and experimental tools. The diplogasterid nematode *Pristionchus pacificus* has been selected for such an analysis because this species shows important developmental differences to *C. elegans*, but simultaneously shares many of its experimental advantages. As a self-fertilizing hermaphrodite *P. pacificus* is amenable to forward and reverse genetic analyses. In addition, a genome map and a genome-sequencing project facilitate functional investigations.⁽²¹⁾

The *P. pacificus* vulva is made by the same three homologous VPCs as the *C. elegans* vulva (Fig. 1B). However, functional studies have revealed various differences in the regulation of vulva development, from which two major conclusions can be drawn. First, the vulva is formed, in part, by non-homologous molecular mechanisms in *P. pacificus* and *C. elegans*. Second, homologous genes have different functions during vulva formation in both organisms. In the following, I will provide three examples supporting these general conclusions.

The Hox gene lin-39

The Hox gene *lin-39* plays a dual role in *C. elegans* vulva formation. First, it specifies the VEG: *Cel-lin-39* mutants do not form a vulva because P3.p–P8.p undergo cell fusion like their anterior and posterior counterparts (Fig. 1C).^(10,11) Second, *Cel-lin-39* is used again later in vulva development in response to vulva induction: *Cel-LIN-39* is one of the key transcription factors that transmits the inductive signal responsible for cell fate specification of P5.p–P7.p (Fig. 1D).⁽²²⁾

The conservation of developmental control genes is considered to represent a general principle in evolutionary developmental biology.⁽²³⁾ As genes are structural entities, they can be homologized based on their primary sequence. *P. pacificus* and *C. elegans* share many homologous genes. *lin-39* was the first gene for which a *P. pacificus* mutation was available allowing detailed investigations of the function of this

gene. *Ppa-lin-39* specifies the VEG in a similar manner as *Cel-lin-39* (Fig. 1C).⁽²⁴⁾ In a *Ppa-lin-39* mutant, P5.p–P8.p adopt the fate of their anterior and posterior neighbors, indicating that LIN-39 has a similar role in both species by preventing the non-vulval fate in the cells of the future VEG. However, inhibition of this non-vulval fate, cell fusion in *C. elegans* and cell death in *P. pacificus*, is achieved by different molecular mechanisms and recent studies revealed that LIN-39 is part of distinct regulatory networks in both species.⁽²⁵⁾ A second major difference is observed when studying the role of LIN-39 in vulva induction: *Ppa-LIN-39* is dispensable for vulva induction, while *Cel-LIN-39* is necessary and sufficient for 1° and 2° cell fate specification in response to EGF (Fig. 1D).^(22,26) Thus, the LIN-39 example indicates that gene function cannot be deduced from sequence similarity and separate functions of a gene can evolve independently from one another, a finding that is neither restricted to nematode vulva formation, nor to *P. pacificus*.

The non-conserved hairy gene and the regulation of the size of the VEG

One major patterning difference between the vulvae of *P. pacificus* and *C. elegans* is the size of the VEG. While in *C. elegans*, six cells P3.p–P8.p are competent to form vulval tissue, only three cells, P5.p–P7.p, are able to do so in *P. pacificus*. Two anterior cells, P3.p and P4.p, die of programmed cell death, thus sharing the fate of their more anterior neighbors, P1.p and P2.p (Fig. 1B). Genetic studies have revealed that a HAIRY/GROUCHO module controls this evolutionary patterning difference by regulating the activity of the Hox gene *Ppa-lin-39* (Fig. 1E).⁽²⁷⁾ Interestingly, the HAIRY/GROUCHO module is absent from *C. elegans*, indicating that differences in the number, structure and function of nematode HAIRY-like transcription factors are involved in the evolutionary modifications of the size of the VEG. More generally, this result provides an example of a molecular specification mechanism that does not only rely on non-homologous genes but even requires the participation of genes in one species that have been lost in others.⁽²⁸⁾

The molecular mechanisms of vulva induction

The inductive signal for *C. elegans* vulva formation is encoded by the gene *lin-3* and represents a member of the epidermal-growth factor family (Fig. 1F,G).⁽¹³⁾ *lin-3*/EGF is expressed in the AC and initiates an EGFR/RAS response in the underlying VPCs. EGF/RAS pathway mutants often show strong vulva-defective phenotypes, whereas mutations in the Wnt pathway result only in mild phenotypes.⁽¹⁵⁾ A discussion about the real function of Wnt signaling in *C. elegans* vulva formation is still ongoing and a recent publication even questions an involvement of Wnt signaling in vulva induction altogether.⁽²⁹⁾

In *P. pacificus*, multiple cells of the somatic gonad have been shown to be required for vulva induction (Fig. 1F).⁽³⁰⁾ Large-scale reverse genetic analysis recently indicated that, in

this species, Wnt signaling has a key role in vulva induction. Mutations in *Ppa-bar-1*, one of two *P. pacificus* β -catenin-like genes, result in a completely vulvaless phenotype, whereas *Cel-bar-1* mutants have a mild vulvaless phenotype (Fig. 1G). Several Wnt ligands have a redundant role in *P. pacificus* vulva induction and double and triple mutants of some Wnt ligand and receptor genes have strong induction-defective phenotypes.⁽³¹⁾ In addition, a Wnt pathway involving *Ppa-lin-17/Fz* functions as a repressor and inhibits vulva formation.⁽³²⁾ These findings revealed an unexpected complexity for Wnt signaling in regulating vulva formation in *P. pacificus*. While some aspects of the molecular mechanism of Wnt signaling in *P. pacificus* vulva induction await further analysis, the comparison to *C. elegans* reveals a much stronger role of Wnt signaling in *P. pacificus*. At the same time, there is so far no evidence for EGF–RAS signaling in *P. pacificus* vulva induction.⁽³¹⁾ The combination of these genetic studies in *P. pacificus* with the extensive phylogenetic reconstruction of vulva evolution^(16,17) led to the speculation that the dominant role of EGF signaling in *C. elegans* vulva induction represents a derived character. One hypothesis would be that the role of EGF signaling coevolved with the restriction of the inductive signal to the single AC.

In summary, these three examples from *P. pacificus* and *C. elegans* vulva formation clearly indicate that the molecular mechanisms underlying the development of homologous structures can differ substantially between species. Future studies will have to identify first, the micro-evolutionary mechanisms that initiate divergence, which finally results in these different macro-evolutionary outcomes and second, the adaptive and non-adaptive forces shaping such evolutionary scenarios.

Homology and function—the caveat of expression studies

Considering the nematode vulva and other examples from the literature, three general conclusions can be drawn.

First, I argue that continuity and hierarchy have to be treated as separate issues of homology. While the continuity perspective of homology considers the “same” structures in different organisms, a hierarchical view connects homology at different levels of biological organization. The vulva is a homologous organ at the morphological level, it is generated by homologous precursor cells, but requires, in part, different cell–cell interactions, non-homologous regulatory networks and molecular modules. Thus, going to smaller biological modules, such as cells, genetic networks or genes can abolish homology, without losing it at the higher biological level. With an increasing emphasis on molecular mechanisms, evolutionary biology will see more such examples in the upcoming decade. We therefore should treat continuity and hierarchy as separate but equally important issues of homology.

de Beer was first to propose that the same (homologous) morphological structure can be build by different genes, but his

monographs from 1958 and 1971 could best be anticipations.^(8,33) Molecular genetic studies of development, like the one on the nematode vulva described here, can now prove this original inference. Wagner (2007) has recently argued that genetic regulatory networks controlling the identity of a given character underlie the homology of morphological structures.⁽⁵⁾ While several aspects of vulva formation support this notion, some key features of vulva evolution tell another story. Both, the signaling networks and the downstream transcription factors involved in providing the identity of vulval cell fates changed during the evolution of *C. elegans* and *P. pacificus* from a last recent common ancestor.

A second conclusion results from the fact that genes are structural entities just like cells, tissues or morphological traits. As such, they can be homologized among organisms, reflecting the continuity of genetic information. The homology of genes across large phylogenetic distances, although not anticipated by evolutionary biologists until very recently,⁽³⁴⁾ represents one of the hallmark findings in molecular biology. Unfortunately, it is often forgotten that, for genes, as for other structural modules, function is of no relevance for homology.^(1,5) Therefore, similar functions provide no evidence for homologous relationships. Among others, studies on insect and vertebrate eye development provide a commemorated example. While original studies based on the common role of the homologous genes *eyeless* (*Drosophila*) and *Pax6* (mouse) suggested the homology of eyes between insects and vertebrates, more detailed investigations revealed striking differences.^(35,36) By now, the conservation of *Pax6*-like genes in eye development throughout the animal kingdom is mostly attributed to this genes' role in the ancestral specification mechanism of photoreceptor cells. Taken together, homologous genes, no matter how strongly they are conserved at the sequence level, can have different functions in different organisms. It is this type of functional changes in the context of structural continuity that drives evolution.

The examples of vulva and eye development and their evolution have however, also to be seen in the light of the complexity of these structures. While many organs in present day species are rather complex entities, they obviously derive from ancestral structures, which contained fewer cell types of limited complexity. The evolution of eyes from simple photoreceptor systems can easily be envisioned, whereas the ancestry of the nematode vulva remains obscure with all current-day species having a vulva and all analyzed species exhibiting a rather similar complexity of the structure.⁽¹⁶⁾ In any case, all morphological structures have evolved from small cellular structures with often simple genetic regulatory networks. When these morphological structures and the underlying networks became more complex, the adaptive and non-adaptive forces shaping evolution often retained the morphological structure, whereas the underlying molecular machinery was to a certain extent free to diverge. This scenario would be

consistent with purifying selection acting stronger at the phenotypic level than at the molecular level. One might speculate that neutral evolutionary processes and other non-adaptive forces play a major role in the evolution of regulatory genes and networks. In a recent synthesis, Michael Lynch (2007) reached a similar conclusion arguing from a population genetic perspective.⁽³⁷⁾ To prove that in the case of vulva evolution—or the evolution of any other developmental trait—non-adaptive forces play a major role, microevolutionary studies and population genetics have to be incorporated with evolutionary developmental biology.⁽³⁸⁾

The final conclusion deals with one of the most-important dualisms in biology, the structure–function dualism. If sequence conservation does not necessarily indicate functional conservation, attempts to deduce function from structure can be highly misleading. This separation of structure and function presents a strong caveat to expression studies, an experimental approach very common in evolutionary developmental biology (evo-devo). Expression pattern analysis of developmental control genes is used in many organisms to reconstruct evolutionary and phylogenetic hypotheses. These studies are often carried out assuming that the function of the analyzed developmental control genes is identical between organisms, an assumption that does not necessarily hold true. The example of eye development in insects and vertebrates cited above is just one of several examples showing that the structure–function assumption is without adequate justification. Therefore, what Owen stated for morphological and anatomical homology is equally true for molecular homology relationships.

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