Dev Genes Evol (2003) 213:149–154
DOI 10.1007/s00427-003-0301-4

HYPOTHESIS PAPER

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Patterns of gene expression: homology or homocracy?

Received: 7 October 2002 / Accepted: 5 January 2003 / Published online: 18 February 2003

Abstract Numerous papers over the years have stated that the original meaning of the term homology is historical and morphological and denotes organs/structures in two or more species derived from the same structure in their latest common ancestor. However, several more recent papers have extended the use of the term to cover organs/structures which are organised through the expression of homologous genes. This usage has created an ambiguity about the meaning of the term, and we propose to remove this by proposing a new term, homocracy, for organs/structures which are organised through the expression of identical patterning genes. We want to emphasise that the terms homologous and homocratic are not mutually exclusive. Many homologous structures are in all probability homocratic, whereas only a small number of homocratic structures are homologous.

Keywords Homology · Homocracy · Evolution · Patterning · Gene

Introduction

The term homologue was introduced by Owen (1843, p. 379) for“the same organ in different animals under every variety of form and function”. This was of course a pre-Darwinian concept, but following Darwin’s (1859) introduction of the theory of biological evolution through common descent, an evolution-based definition has been adopted, because as formulated succinctly by Dobzhansky (1973)“nothing in biology makes sense except in the light of evolution.” Both Owen and Darwin based their studies on morphology, and a modern, morphology-based, phylogenetic (or historical) definition of homologous structures could be:“homologous structures in two or more taxa are structures derived from the same structure in their latest common ancestor”. It should be emphasised that with this definition, homology is an idealistic concept, and that many different methods can be (and have been) used in attempts to identify homology and thereby ultimately give information about phylogeny (see for example Hall 1994). Many types of characters have been used in attempts to identify homologies. Traditional morphological (and embryological) characters are still at the centre of the studies (Nielsen 2001), and similar considerations can be applied to the“morphology” of molecules. Here, we will discuss characters derived from studies of gene expression. The question here is whether morphological homology can be inferred just from expression of genes/gene batteries, as suggested by a number of authors. This question has also been discussed by, for example, Abouheif et al. (1997), Tabin et al. (1999) and Gould (2002).

Edited by R. Sommer

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Gene activity during development

Many genes are active during development at different times and in different tissues or cells, participating in genetic interactions with other genes (genetic networks). Generally, this is realised in multiple traits affected by a single gene mutation (pleiotropy). The complexity of genetic interactions in which a gene participates is reflected in its *cis*-regulatory apparatus (Davidson et al. 2002). There, the different inputs to which the gene responds during development become integrated; hence complex *cis*-regulatory regions normally reflect complex inputs and complex expression patterns. A consequence of this fact is that differences in the expression patterns of specific genes in different species may be brought about just by changes in their *cis*-regulatory sequences or their *trans*-acting factors (Belting et al. 1998; Ackerman et al. 2002). Such changes have occurred many times during the evolutionary history of animals (Lowe and Wray 1997; Ludwig et al. 2000; Tautz 2000) giving rise to the redeployment of gene activities into new spatio-temporal domains (co-option).

It is, therefore, important to point out that the domains of gene expression in two (or more) different organisms do not necessarily reflect common descent of the structures involved. Of course, a stronger case would be made by the use of synexpression groups (Niehrs and Pollet 1999) or gene regulatory networks (Davidson 2001).

In the following sections we review a few, well-described cases of patterning genes and how their expression domains have been used (sometimes misused) to assess structural homologies in different taxa.

Distal-less

The *Distal-less* (*Dll,* or *Dlx* in vertebrates; see Fig. 1) gene encodes a homeobox-containing transcription factor. It is present as a single copy in most invertebrate groups analysed (with the exception of ascidians; Caracciolo et al. 2000) and in multiple copies in all vertebrates (Zerucha and Ekker 2000). Where multiple copies of *Distal-less* exist, they appear organised in tandems of two genes each. In vertebrates, each pair is specifically linked to a unique *HOX* cluster locus.

Dll/Dlx genes have been analysed in a wide variety of animal groups, including nematodes (*Caenorhabditis*; Aspock and Burglin 2001); arthropods, chelicerates (*Limulus* – horseshoe-crab, Mittmann and Scholtz 2001; *Cupiennius* – spider, Schoppmeier and Damen 2001), crustaceans (*Triops* – branchiopod, Williams et al. 2002), and insects (*Schistocerca* – grasshopper, Jockusch et al. 2000; *Drosophila* – fly, Cohen et al. 1989; *Bicyclus* – butterfly, Beldade et al. 2002; *Tribolium* – beetle, Beerman et al. 2001); molluscs (*Mopalia*, *Kelletia*, Lee and Jacobs 1999); echinoderms (*Strongylocentrotus*, *Cucumaria*, *Evasterias*, Lowe et al. 2002); enteropneusts (*Ptychodera*, Harada et al. 2001); urochordates (*Ciona*, Caracciolo et al. 2000); cephalochordates (*Branchiostoma*, Holland et al. 1996); and different vertebrates (Neidert et al. 2001; Quint et al. 2000). Recently, a sequence has also been obtained from a cnidarian (*Chlorohydra*, Gauchat et al. 2000).

Initially, *Distal-less* was characterised in *Drosophila*, where mutants showed size reduction and loss of distal structures in the legs (Cohen et al. 1989). A specific antibody raised against the *Dll* protein of the butterfly *Precis coenia* (Panganiban et al. 1997) is cross-reactive among phyla and has allowed a more detailed analysis of *Dll* activities in other bilaterian systems. Strikingly, it has been shown that *Dll* genes are expressed in the distal tips of many“outgrowths” in such different animals as insects, echinoderms and vertebrates. That prompted Panganiban et al. (1997) to propose that the genetic machinery responsible for growing appendages may have been present in the bilaterian ancestor (and, perhaps, even the appendages themselves). More recently, genetic analyses of *Dll* mutants in two arthropod groups (insects and spiders) has shown that the lack of *Dll* protein leads to a similar loss of terminal appendicular structures. Moreover, mutant *Tribolium* larvae lacked all head appendages that are regarded as limbs (antennae, the labrum and the labial and maxillary palps), while the mandibles were unaffected (Beermann et al. 2001). In spiders the labrum was also missing as well as the prosomal appendages (pedipalps, cheliceres and all walking legs). Though these arthropod appendages differ morphologically and developmentally in important ways it seems that all depend on *Dll* for proper P/D patterning. Intraphyletic homologies between the structures that express *Dll* are more dubious (not to mention interphyletic comparisons). The expression domains of *Dll* in arthropods (Abzhanov and Kaufmann 2000; Williams et al. 2002) do not map to any particular morphological domain (as suggested, for instance, by Gonzalez-Crespo and Morata 1996), they just specify the distal tips of many appendages (used as a developmental patterning tool, as suggested by Williams et al. 2002). In fact, it seems that the patterning of the whole P/D axis in arthropod limbs uses a similar, but not identical, set of genes (Prpic et al. 2001).

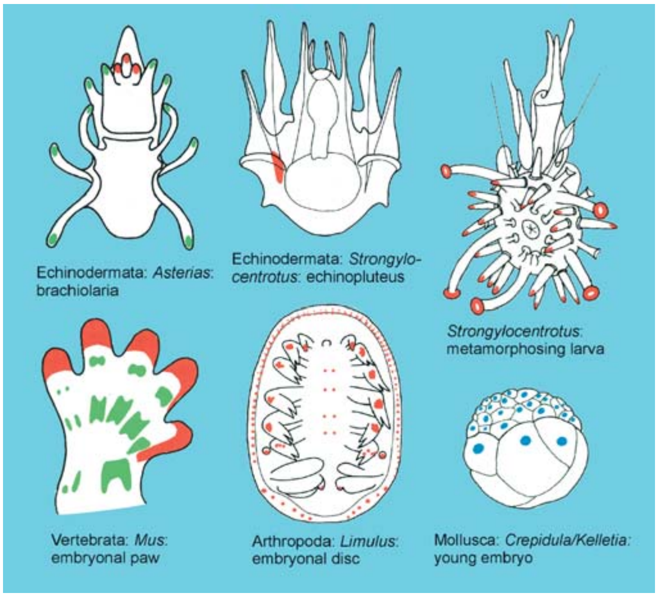

Fig. 1 Expression of the gene *Distal-less* (*Dll/Dlx*) in obviously non-homologous structures in embryos or larvae of various taxa. *Blue* expression in all nuclei; *red* expression in ectoderm; *green* expression in mesoderm. Echinodermata: *Evasterias* brachiolaria larva, based on Kaestner (1963; morphology of *Asterias*) and Lowe and Wray (1997; gene expression); *Strongylocentrotus* echinopluteus larva, based on Czihak (1960; morphology of *Psammechinus*) and Lowe and Wray (1997; gene expression); *Strongylocentrotus* metamorphosing larva, based on Czihak (1960; morphology of *Psammechinus*) and Lowe and Wray (1997; gene expression). Vertebrata: *Mus* paw of an embryo, based on Merlo et al. (2000). Arthropoda: *Limulus* based on Kishinoye (1891; morphology) and Mittmann and Scholtz (2001; gene expression). Mollusca: embryo combined from drawing of *Crepidula* (Conklin 1897) and gene expression in *Kelletia* (Lee and Jacobs 1999).

Distal-less is also expressed in sensory organs during arthropod development (Mittmann and Scholtz 2001). Since sensory organs are located in the limbs, it was suggested that the role of the different arthropods' *Dll* gene may reflect the role of *Dll* in sensory organ specification/differentiation. A primitive role in sense organ specification seems more plausible. Later, *Dll* could have become co-opted in different bilaterian lineages for the morphogenesis of the limbs (and other outgrowing structures).

It is obviously more difficult to draw conclusions from comparative analyses of *Dll* expression in different phyla. Identification of a pan-bilaterian role for *Dll* seems almost out of reach. Molluscs seem to use *Dll* early in development (pregastrulation) for patterning of the animal-vegetal axis and later on to specify regions of the ectoderm (Lee and Jacobs 1999). In the nematode *Caenorhabditis elegans*, the product of the *Dll* ortholog gene *ceh-43* is mainly localised in the head hypodermis and the neuronal support cells (Aspock and Burglin 2001). *Ceh-43* mutant embryos show specific phenotypes: leaking of cells, tail deformation and detached pharynx (consistent with having defects in the head and tail hypodermal epithelium). Based on the molluscan and nematode expression patterns a more general role for *Dll* has been proposed, both in the development of epithelial structures (epithelial expression is also seen in deuterostomes, Morasso et al. 1995; Lowe et al. 2002; and *Drosophila*, Cohen 1990), and perhaps also in neurogenesis (vertebrates, see Merlo et al. 2000; invertebrates, see Panganiban 2000). Again, expression could be associated with the formation of sensory organs (Mittmann and Scholtz 2001).

The analysis of chordate *Distal-less* ortholog gene expression is complicated by the presence of multiple copies. There is a single *Dll* gene detected in the cephalochordate amphioxus (Holland et al. 1996), whereas urochordates have three (Caracciolo et al. 2000) and vertebrates six copies. Amphioxus *Dll* is expressed first in the presumptive ectoderm, during gastrulation, and later on in neural cells through neurulation. During this last phase, the neural cells expressing *AmphiDll* occupy the anterior part of the cerebral vesicle. Since craniate embryos express *Dlx* genes in the forebrain (Price et al. 1991; Akimenko et al. 1994) it has been assumed that the most anterior neural tube in amphioxus represents a region homologous to the craniate forebrain (Holland et al. 1996). This is supported by the fact that other regulatory genes expressed in vertebrate forebrain are also expressed in the most anterior neural tube of amphioxus (Schilling and Knight 2001).

Ascidian *Distal-less* genes seem to be devoted to the construction of phylum-specific structures (the atrial siphon and the adhesive organ) and are therefore difficult to relate to the domains observed in cephalochordates and vertebrates (Caracciolo et al. 2000).

Vertebrates express the several *Dlx* relatives in complex patterns that include craniofacial, sensory (otic and optic placodes) and brain-derived (forebrain and olfactory bulb) structures (Merlo et al. 2000). Interestingly, some of them are expressed in the apical ectodermal ridge, AER, located in the distal portion of limbs and in other"outgrowing" structures such as ear lobes and genital buds (Merlo et al. 2000). The expression pattern is reminiscent of the pattern observed in the limbs (or buds) of other animal groups (Panganiban et al.1997; Gorfinkiel et al. 1999). *Dlx5* and *Dlx6* knockout mice show loss of digits, a direct effect of a decrease of cell proliferation in the AER (Robledo et al. 2002). Though it seems unquestionable that arthropod and vertebrate limbs are not morphologically and developmentally homologous, the expression of *Dlx* may point to some very general properties of this gene in limb formation, namely a general regulator of proliferation. Other authors have suggested that a role could be the regulation of adhesion-related genes (Aspock and Burglin 2001). As there are no known direct targets of *Dll* regulation identified so far, it is difficult to envisage a more concrete gene activity model.

Thus, the commonalties shared by the expression of the *Distal-less* gene (or any other) between phylogenetically distant groups of organisms turn out to be few and very general. It becomes difficult to use gene expression domains as useful tools to analyse homologies unless closely related groups are considered. In this context, a paradigmatic case is presented by Lowe et al. (2002), who analysed the expression of *Distal-less* in several echinoderms. They clearly showed that regulatory genes such as *Distal-less* can change functions (become co-opted) very rapidly, even within a single phylum, reflecting morphological and life history changes.

Pax-6/eyeless

The *Pax-6/eyeless* gene is a homeobox gene that has been found to control the development of a number of organs in vertebrates, such as brain, including olfactory bulbs (Callaerts et al. 2001) and certain secretory cells in the gut (Larsson et al. 1998), and eyes in vertebrates and a number of invertebrates, such as insects and molluscs (see below). Elegant experiments have shown that *Pax-6* can induce the development of ectopic eyes, for example on legs and antennae in *Drosophila*, and it has also been shown, for example, that squid *Pax-6* is able to induce the development of ectopic eyes in *Drosophila* (Tomarev et al. 1997). However, in regenerating planarians the expression of *Pax-6* orthologs in eye spots seems to be irrelevant for their cell specification (Pineda et al. 2002). It seems unquestionable that the eyes and the just-mentioned nasal and gut structures are not historically homologous, but it is hotly debated whether all animal eyes are homologous, as strongly argued by Gehring (see for example Gehring and Ikeo 1999; Gehring 2002).

Eyes on the mantle edge of bivalves show many different morphological types; simple cup eyes of both everse and inverse types are found, and the eyes of *Pecten* have a layer of rhabdomeric and one of ciliary sensory cells. Sabellid polychaetes have compound eyes on the tentacles and compound eyes are found on the mantle edge of arcoid bivalves (Nilsson 1994). To our knowledge, it has not been shown that *Pax-6* is involved in inducing the formation of these non-cerebral eyes. It seems clear that these eyes cannot be historically homologous with the cerebral eyes, but must have evolved independently in a number of lineages. Non-cerebral eyes are also found on the edge of the bell of several medusae, including the large and complex eye of the cubomedusae *Tripedalia* and *Chironex* (Piatigorsky et al. 1989; Gehring 2002), but *Pax-6* has not been detected in any cnidarian (Miller et al. 2000).

The enormous morphological variation, simple/compound, everse/inverse, ciliary/rhabdomeric, does not indicate that all these eyes are derived from one ancestral type (Nilsson 1990, 1996; Oakley and Cunningham 2002), and their scattered distribution among the bilaterians indicates multiple origins too. Nilsson and Pelger (1994) have calculated that a camera-type eye with a lens can evolve from a flat, photosensitive epithelium during less than 500,000 generations. *Pax-6* and a number of other genes involved in eye formation (see for example Carosa et al. 2002) have been co-opted many times into building molecules which are organised in different ways in the many different types of eyes. So if most of the genes involved in organising various types of eyes are ancient, and this seems probable, and also because only a very limited number of genes are actually available, it appears that the same genes have been co-opted for similar functions many times, giving rise to the many, morphologically quite different eyes found among the metazoans.

Thus, *Pax-6* is not a prerequisite for the formation of eyes and the gene is expressed in eyes which are not historically homologous, so gene expression cannot be used to infer phylogenetic homology of animal eyes.

Genes related to heart/pharynx development

Haun et al. (1998, p. 5072) pointed out that “development of pharyngeal muscle in nematodes (*Caenorhabditis*) and cardiac muscle in vertebrates (*Mus*) and insects (*Drosophila*) involves the related homeobox genes *ceh-22*, *nkx2.5*, and *tinman*, respectively.” A considerable degree of sequence identity was demonstrated between the *ceh-22* and *nkx2.5* proteins, and it was found that *nkx2.5* can substitute for *ceh-22* in loss-of-function mutant *Caenorhabditis*. This was taken to indicate that an ancient molecular mechanism is involved in organising the two contractile tubular structures. Maduro et al. (2001, p. 475) went a step further in stating about *Caenorhabditis* that “... the posterior part of the pharynx feeding organ ... appears to be homologous to the vertebrate heart ...” and Rodaway and Patient (2001, p. 171) directly suggested that the vertebrate heart and nematode pharynx are homologous. However, it must be emphasised that the nematode pharynx is an ectodermal structure (a so-called myoepithelium where the epithelial cells contain myofilaments) which pumps food particles, whereas the hearts of insects and vertebrates are mesodermal structures which pump blood, so neither embryological origin nor adult structure and function of the two organs show any indication of phylogenetic homology.

Conclusion

The value of the traditional, morphology based, phylogenetic definition of homology has been demonstrated through numerous studies. Several studies of morphology and developmental genetics have come to the conclusion that gene expression alone cannot indicate homology, see for example Tautz (1998), Tabin et al. (1999) and Gould (2002). We believe that these studies and the examples discussed earlier are representative of the field of developmental biology, and in accord with several earlier authors we conclude that it can only bring confusion if the traditional homology concept is extended to cover structures identified by similar gene expression. It appears that a term for structures organised through expression of homologous genes is needed, and we here propose the new term homocracy (see Definitions below) to describe organs/structures which show similar gene expression patterns in two or more species.

The homocratic structures are built using similar developmental processes. Since the available genetic “toolbox” is of limited size there is always a clear, distinct possibility of convergence. Thus, as emphasised recently by Gilbert and Bolker (2001), we should keep in mind that“commonalities of process, however, do not render the various structures homologous.”

Definitions: Homology and homocracy

The classical homology concept has in recent years become corrupted by use in a number of non-anatomical fields. We here propose a new term to remove some of the ambiguity.

Homology

Structures/organs are homologous if they are derived from the same structure/organ in their latest common ancestor. This definition can also be used about proteins and genes.

Homocracy

Structures/organs are homocratic if they share the expression of the same patterning gene(s). (Homocracy, from Greek: same-government; pronunciation like democracy, democratic)

Homocratic structures may be homologous, but a gene may have"successive roles" in organising various, obviously non-homologous structures in an embryo (Holland et al. 1996), and the same gene may be organising other obviously non-homologous structures in different organisms (see Fig. 1). Homologous structures are homocratic in many cases, but it remains to be seen how far this is valid across the animal kingdom.

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