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Evolution of the vertebrate jaw: homology and developmental constraints

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Abstract. In embryonic development of the vertebrate head, neural crest-derived ectomesenchyme contributes to a wide range of tissue types including oro-pharyngeal and ethmoidal cartilages. The evolution of the jaw, therefore, can be viewed as a change of developmental program for specification of the crest cells. Along the anteroposterior axis of the neural crest of amniote embryos, a series of homeobox genes are expressed in a nested pattern, and the jaw-forming mandibular arch receives crest cells expressing no *Hox* genes and midbrain-derived crest cells that express *Otx2*. Cognates of these regulatory genes are present in the lamprey, and are expressed in the comparable cell lineages of the embryo. Evolution of the jaw cannot be explained from such shared developmental mechanisms, but rather noncomparable elements have to be sought, if the jaw is truly an evolutionary novelty. By precise comparative morphology and gene expression analyses, a possibility was inferred that ammocoete lips may not be identical to gnathostome jaws.

Key words: embryology, jaw evolution, lamprey, neural crest, pharyngeal arches, regulatory genes

Evolutionary developmental biology of jaw

Origin of the vertebrate jaw has long been an intriguing issue of vertebrate morphology. Recently, molecular developmental data have opened a new possibility to solve this problem. Combined with comparative embryology, this field has introduced a new approach to the understanding of the evolution of form. This review is intended to discuss the contribution Evolutionary Developmental (Evo-Devo) studies could make to the understanding of the jaw and the possibility that it is an evolutionary novelty. For this purpose, lampreys are the only agnathan animals that are embryologically accessible among the extant vertebrate species for comparison. As the sister group of gnathostomes, developmental patterns of the lamprey will indicate gnathostome-specific features potentially associated with the invention of the jaw.

The jaw is generally accepted to be an early invention in the evolutionary history of the Vertebrata, and is believed to have been derived from the mandibular arch, the rostralmost pharyngeal arch element (reviewed by Goodrich, 1930; de Beer, 1937; Jollie, 1962; Moy-Thomas and Miles, 1971; Mallatt, 1996; Janvier, 1996; and by Kimmel *et al.*, 2001; also see Jarvik, 1980 for modified views). The hypothetical ancestral animal is assumed to have possessed an undifferentiated series of pharyngeal arches, and the jaw was thought to have arisen as a consequence of position-specific transformation of the arches. The novelty of the jaw, however, has not been extensively evaluated.

Many fossil agnathans and even the ammocoete larva of the lamprey possess well differentiated protrusions on the dorsal and ventral edges of the mouth, and dorsoventral differentiation in itself is not innovative (Figure 1; reviewed by Mallatt, 1996; Kuratani *et al.*, 2001). Instead, evolutionary innovation or novelty in the strict sense refers to a newly acquired pattern that is not directly comparable to that of the ancestral animals (Müller and Wagner, 1991; Wagner and Müller, 2002; also see Eberhard, 2002). For example, chiropteran wings can be regarded as a modification (adaptation) of the mammalian forelimb, since both structures are comparable in terms of topographical arrangement of anatomical elements such as bones and muscles. In this example, morphological and biological homologies (Wagner, 1994) are preserved as the consequence of developmental constraints. On the other hand, the rib of the turtle, or the primary component of the shell, develops in the superficial layer of the body wall, dorsal to the scapula, and epi- and hypaxial muscles are missing, unlike other amniotes. The morphological pattern of the turtle shell, therefore, cannot be obtained by simple modification of the canonical amniote plan (Hall, 1998; Gilbert *et al.*, 2001;

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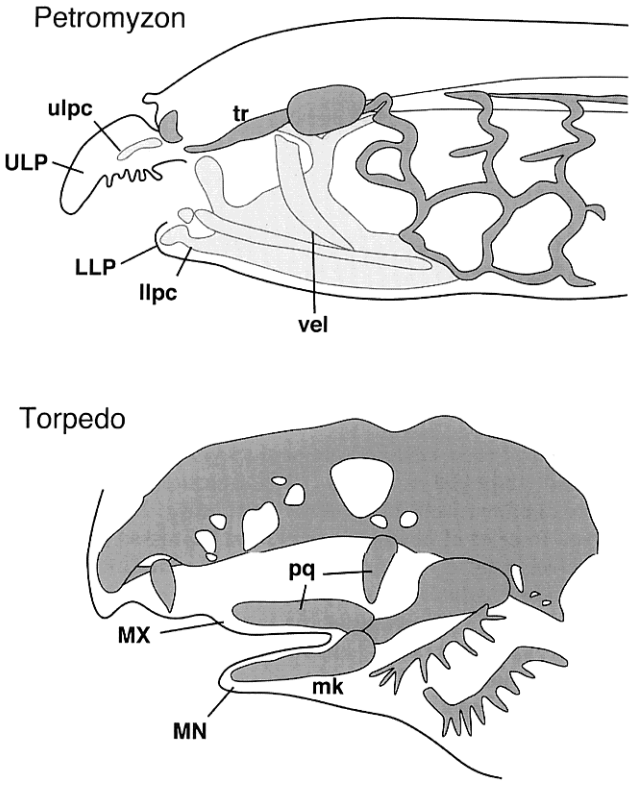


Figure 1. Comparison of the chondrocranium in the ammocoete larva of the lamprey and gnathostome embryo. Above: Chondrocranium of the *Petromyzon* larva. Lightly colored portion represents the mucocartilage (reviewed by Hall, 1999). Note that the oral region of this animal is well differentiated, and the mouth is fringed by dorsal and ventral protrusions (upper and lower lips) reminiscent of jaws of gnathostomes. Velum is the pumping apparatus of the lamprey functioning in water inlet into the pharynx. This structure also contains a cartilaginous bar that develops in the wall between the pharyngeal endoderm and oral ectoderm. Below: Chondrocranium of *Torpedo* embryo. The mandibular arch is divided into dorsal and ventral halves, differentiating cartilages in the upper jaw (palatoquadrate) and lower jaw (Meckel's cartilage), respectively. Abbreviations: *LLP*, lower lip; *llpc*, lower lip cartilage; *mk*, Meckel' s cartilage; *MN*, mandibular process or the lower jaw; *MX*, maxillary process or the lower jaw; *pq*, palatoquadrate; *tr*, trabecula of the lamprey; *ULP*, upper lip; *ulpc*, upper lip cartilage; *vel*, velum. Modified from de Beer (1937).

Loredo *et al.*, 2001). The newly achieved pattern in the turtle is thus not obtained through local enlargement or shrinkage, but, we should rather assume, through modification of the standard amniote developmental pattern for carapace evolution. Likewise, if the vertebrate jaw is comparable (homologous) to every element of the agnathan oral apparatus, it will turn out to be a mere modification (adaptation) of the agnathan mouth and not deserve the status of a novelty (Müller and Wagner, 1991; Wagner and Müller; 2002). Here lies a central dilemma of comparative morphology; truly innovative and radical structures may not permit comparison with the ancestral pattern since the morphological homology may have already been lost.

In the lamprey oral apparatus, dorsal and ventral protrusions, called upper and lower lips, respectively (Figure 1), are recognized in the larval state. To understand the jaw evolution, therefore, the first step is to determine whether agnathan oral lips or plates are homologous to jaws or not. Although the homology of branchial arches between the lamprey and gnathostome fish has often been questioned, that of the jaw has not been explicitly raised so far.

Phylotype, or general morphology of vertebrates

Whether they possess a jaw or not, vertebrate embryos exhibit a stereotyped pattern of morphology at the organogenetic stage of development. This stage, called the pharyngula, is characterized by the presence of pharyngeal arches, somites and a segmented neural tube, which are regarded as the developmental units for the vertebrate body plan (Figure 2). Thus, the pharyngula is also called the 'phylotype' of vertebrates (reviewed by Hall, 1998). According to Raff (1996), the conserved morphology of the pharyngula is an evolutionary prerequisite, which can be ascribed to high levels of developmental constraints that are necessary for a number of global interactions occurring at the organogenetic stage.

Embryology of lamprey species has revealed highly conserved morphological patterns of development comparable to gnathostomes (Koltzoff, 1901; Damas, 1944; reviewed by Kuratani *et al.*, 2001). These include configuration of the mesoderm (cephalic mesoderm and somites; Kuratani *et al.*, 1999), global deployment of cephalic crest cells (see below; Horigome *et al.*, 1999), segmental pattern of the neural tube (Kuratani *et al.*, 1998b), cranial and spinal nerves (Kuratani *et al.*, 1997), and basic morphology of the brain (Kuratani *et al.*, 1998b; Murakami *et al.*, 2001). All of these shared traits constitute the vertebrate phylotype, and thus the origin of these patterns is very old, predating, we must assume, the common surmised Cambrian ancestor of gnathostomes and the lamprey (Shu *et al.*, 1999; Holland and Chen, 2001). Conserved embryonic morphology is often associated with conserved expression patterns of regulatory genes (see below).

One of the important synapomorphies of vertebrates is the contribution of the neural crest-derived ectomesenchyme to organogenesis (Gans and Northcutt, 1983; Northcutt and Gans, 1983; reviewed by Maderson, 1987; Hall and Hörstadius, 1998; and by Hall, 1999). The neural crest is induced at the junction of the neural plate and surface ectoderm at neurula stage, the cells within the crest deepithelialize around the stage of neurulation, and they migrate along specific pathways in the embryonic body to differentiate into various tissue types (reviewed by Le

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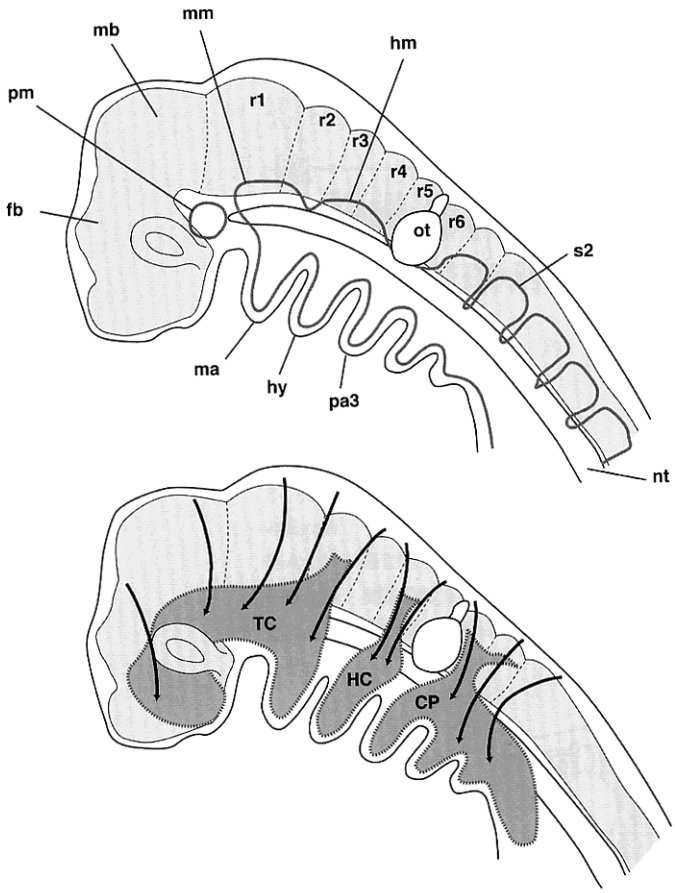


Figure 2. Generalized morphology of the vertebrate pharyngula. At the pharyngula stage of development, vertebrate embryos resemble each other, consisting of similarly patterned cell populations and germ layers. Above: Neural tube, notochord, and the mesoderm are schematically shown. Somites, or the real segmentation of the mesoderm, are only seen caudal to the otic vesicle. Rostral to the vesicle, the mesoderm is called the head mesoderm, which is unsegmented possibly except for the premandibular mesoderm that develops directly from the prechordal plate. Below: Migration streams and distribution patterns of cephalic crest cells are shown. Crest cells are thought to be roughly specified along the antero-posterior neuraxis. Three crest cell populations are recognized in the head, termed, from rostral to caudal direction, trigeminal, hyoid, and circumpharyngeal crest cells. Mandibular arch skeletons arise from a part of the trigeminal crest cells that extends to both the mandibular and premandibular regions. Abbreviations: *CP*, circumpharyngeal crest cells; *fb*, forebrain; *hb*, hindbrain; *HC*, hyoid crest cells; *hm*, hyoid mesoderm; *hy*, hyoid arch; *ma*, mandibular arch; *mb*, midbrain; *mm*, mandibular mesoderm; *nt*, notochord; *ot*, otic vesicle; *pa3*, pharyngeal arch 3; *pm*, premandibular mesoderm; *r1–6*, rhombomeres (numbered); *s2*, second somite; *TC*, trigeminal crest cells.

Douarin, 1982). Especially in the head of vertebrates, the majority of the ventral mesenchyme is of Cephalic-crest origin and is called the ectomesenchyme. This mesenchyme is actually the source of jaw and branchial arch cartilages, or the splanchnocranium in gnathostomes (reviewed by Le Douarin, 1982; and by Noden, 1988). Although the posterior neurocranium (brain case) is derived from the cephalic mesoderm (Couly *et al.*, 1993; reviewed by Noden, 1988), it is still controversial whether the dermal calvarium is derived from the neural crest or the mesoderm (Noden, 1988; Couly *et al.*, 1993; Iseki *et al.*, 1999; Morriss-Kay *et al.*, 2001). The rostral half of the neurocranium (sphenethmoidal region) is also derived from the neural crest. Thus, the vertebrate head has two types of mesenchyme (mesoderm and ectomesenchyme), which apparently differentiate into anatomically distinct types of skeletons (reviewed by Noden, 1988; Kuratani *et al.*, 1998a; but see Schneider, 1999).

A neural crest has been observed in all the vertebrate embryos examined so far, including the lungfish which was once thought to lack the crest, and the lamprey (Falck *et al.*, 2000; Horigome *et al.*, 1999 and references therein). Not much is known about the crest in hagfish (Dean, 1899), but neural crest-like structures have been identified (Conel, 1942 ; reviewed by Hall, 1999). In the lamprey, although there is no direct evidence to show that the neural crest is the source of oral- and branchial-arch cartilages, the distribution pattern of the putative ectomesenchyme within the pharyngeal arches of the larval lamprey prefigures the site of cartilage formation including that of the lamprey-specific mucocartilage (Horigome *et al.*, 1999; Kimmel *et al.*, 2001; see Gaskell, 1908 and Hall, 1999 and references therein for the mucocartilage). Ectopic transplantation of the lamprey neural crest once suggested the chondrogenic activity of the lamprey crest (Newth, 1956), which has recently been questioned by Hall (1999). Newth (1951), as well as Langill and Hall (1988) have performed ablation of the lamprey cephalic crest at the neurula stage, and the splanchnic cartilage was observed to be reduced in later development. Although the anatomy of the gill arches shows distinct differences between the lamprey and gnathostomes (Gegenbaur, 1898; Jarvik, 1964, 1968), the crest origin of the branchial cartilage appears to be shared between these animals, as the morphological pattern can be compared by thorough comparison of anatomical components (Mallatt, 1984; but also see Kimmel *et al.*, 2001).

Neural crest, gene expression and jaw development

In the first step of jaw development in gnathostomes, neural crest-derived cells migrate ventrally to fill the pharyngeal arch to form the pharyngeal ectomesenchyme (Figure 2, below). Along the antero-posterior (A-P) axis of the neural crest, the premigratory cells are already roughly specified as to which region of the pharynx they are destined (reviewed by Hall, 1999; and by Graham,

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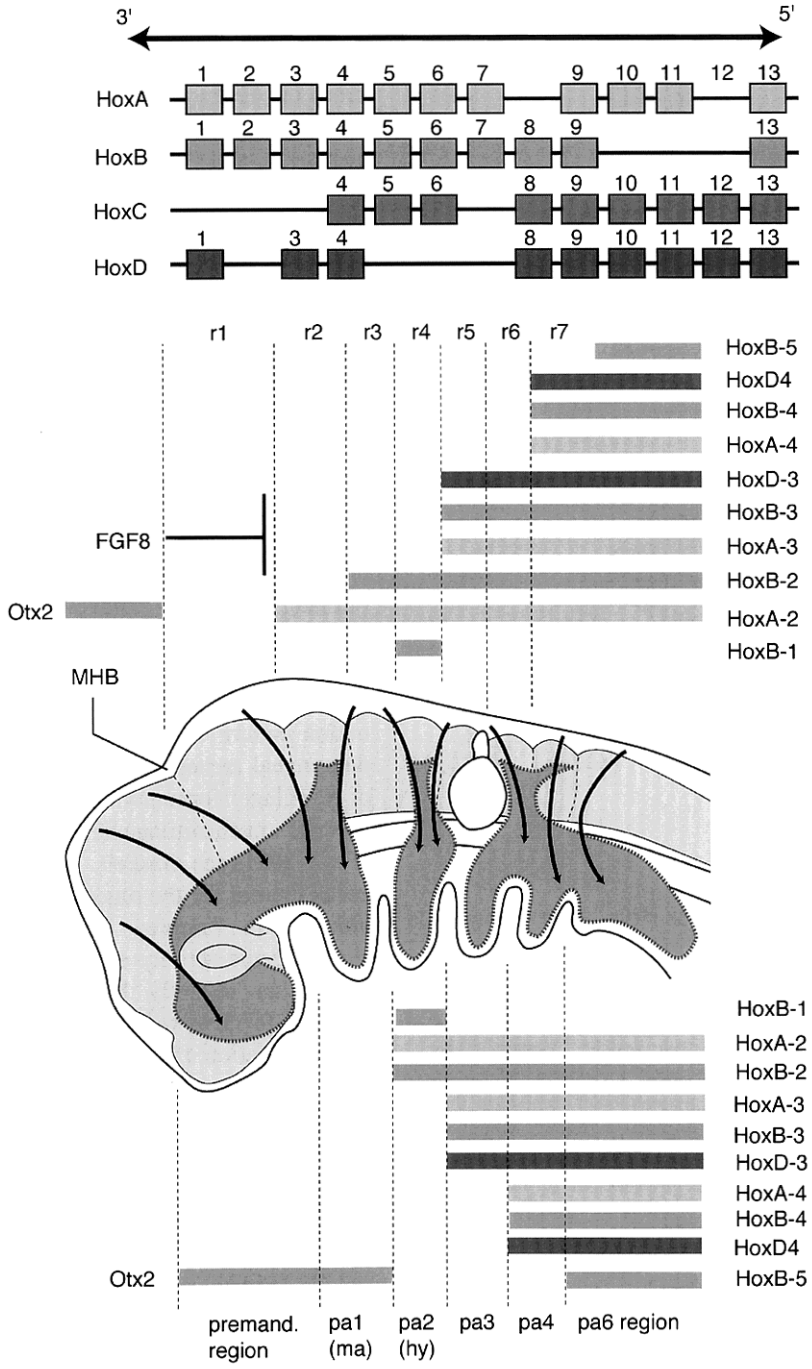


Figure 3. *Hox* gene clusters and cephalic *Hox* code in the vertebrate pharyngula. Above: Non-teleost gnathostomes possess four *Hox* clusters on different chromosomes. Within a cluster, genes located in the 3' part of the clusters are likely to be upregulated earlier and more anteriorly in the embryo. Below: *Hox* genes are expressed along the anteroposterior axis of the embryo with a nested pattern. Along the axis of the neural tube, *Hox* gene expression domains have rostral boundaries that correspond to the boundaries of rhombomeres, the metamerical bulges in the hindbrain. At the mid-hindbrain boundary is the source of the secreted protein, FGF8, which has been shown to suppress the *Hox* regulation in the vicinity. Rostral to the boundary, another type of homeobox gene, *Otx2*, is expressed rostrally. Below the embryo is shown the expression map of homeobox genes in the ectomesenchyme. Here again, the *Hox* genes are expressed in a nested fashion and in each pharyngeal arch the ectomesenchyme possesses its specific set of *Hox* genes, thus position-specific differentiation is thought to be achieved in the pharyngeal arches. The mandibular arch receives crest cells that express *Otx2* gene but no *Hox* genes, and this arch is patterned partly by the default state of the *Hox* code. It has also been shown that *Otx2* is prerequisite for the normal patterning of the lower jaw. Abbreviations: *hy*, hyoid arch; *ma*, mandibular arch; *MHB*, mid-hindbrain boundary; *pa1–6*; pharyngeal arch 1 to 6 region; *r1–7*, rhombomeres (numbered).

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2001). For example, the neural crest at the hindbrain level is segmented into bulges called rhombomeres and the crest cells filling the mandibular arch originate from the midbrain to the third rhombomere (Figure 2). The neural crest ranging from rhombomere 3 through 5 gives rise to cells migrating into the second (hyoid arch), and the third arch receives cells from rhombomere 5 and posterior, and so forth (Figure 2, below; Köntges and Lumsden, 1996). Similar specification of the mid-hindbrain crest has also been observed in the lamprey (Langill and Hall, 1988; Horigome *et al.*, 1999).

The A-P specification of the mid-hindbrain crest is crucial for the molecular-level shaping mechanism of the splanchnocranium. A series of homeobox-containing genes, the *Hox* genes, are expressed along the neural tube in a nested pattern, and crest-derived ectomesenchyme also expresses similar sets of *Hox* genes (Figure 3; Hunt *et al.*, 1991; McGinnis and Krumlauf, 1992). By establishing the coordinated expression patterns of *Hox* genes (*Hox* code; Figure 3; Hunt *et al.*, 1991), each part of the cephalic ectomesenchyme acquires its specific combination of *Hox* gene transcripts. Since the *Hox* genes encode transcription factors, ectomesenchyme in each pharyngeal arch is thought to be under position-specific developmental control, possibly exemplifying the molecular bases for segmental metamorphosis of the pharyngeal arch evolution (reviewed by Kuratani *et al.*, 1998a).

Hox genes are arranged tandemly in four clusters (*Hoxa* to *d*) on four different chromosomes of amniotes. Within each cluster, 3'-located genes tend to be transcribed earlier and in a more rostral part of the embryo whereas the genes to the 5' side of the cluster are regulated later in development at a posterior position along the embryonic axis (Figure 3). Thus, there are spatiotemporal colinearities between the arrangement of the *Hox* genes on the DNA and regulation of the *Hox* genes.

Genes occupying the same relative positions of the clusters are called paralogues, referring to homologous genes generated by gene duplications. Paralogue groups 1 and 2 genes are expressed in the hyoid arch and posterior arches, and paralogue 3 genes in the third arch and posterior (Figure 3). There is no *Hox* gene expressed in the mandibular arch. Thus, the jaw patterning is thought to be based on the default state of the *Hox* code (see below). The nested expression pattern of *Hox* genes, the *Hox* code, is very clearly seen at the phylotypic stage (reviewed by Duboule, 1994). Although *Hox* gene expression has not been reported in the lamprey except for the analysis of its regulation on transgenic mice, rhombomeres and brain compartment-specific gene expression have been observed (Holland *et al.*, 1993; Kuratani *et al.*, 1998b; Ueki *et al.*, 1998; Horigome *et al.*, 1999; Myojin *et al.*, 2001; Murakami *et al.*, 2001).

Function of the *Hox* gene in cephalic skeletal patterning had already been implied in experimental embryology before the genes themselves were discovered. By heterotopic transplantation of the jaw-forming crest into the hyoid level, Noden (1983) found that the morphological identity of the mandibular arch was already set up in the premigratory crest, and was maintained after translocation to an ectopic site. Similarly, it was shown that species-specific morphology of the mandibular arch skeleton also resides in the premigratory crest based on transplantation experiments in amphibian embryos (Wagner, 1949, 1959; reviewed by Noden, 1988). These experiments apparently parallel the cell-autonomous expression of *Hox* genes in rhombomeres (Kuratani and Eichele, 1993), and also the gene-targeting experiment of *Hoxa2* in the mouse (Figure 4; Rijli *et al.*, 1993; Gendron-Maguire *et al.*, 1993); if *Hoxa2* is disrupted the *Hox* code of the mutant hyoid arch resembles that of the mandibular, and as expected, the mandibular arch identity was duplicated in the hyoid level of the mutant mouse. The cephalic *Hox* code thus appears to be the basis for metameric transformation of the branchial arch in gnathostomes. Expression and function of the *Hoxa2* homologue in the lamprey is thus an intriguing issue.

Unlike the above scenario, it has recently come to light that *Hox* gene expression in the crest cells does not rely entirely on their origin along the neural crest. In addition to the upregulation at the premigratory state (Kuratani and Eichele, 1993), the stable ectomesenchymal expression of the *Hox* genes appears to be regulated through the community effect of the crest cells themselves as well as induction by the embryonic environment (Itasaki *et al.*, 1996; Goul *et al.*, 1998). Thus, the maintenance of the *Hox* code appears to be under the epigenetic control of the pharyngula. This idea obviously contradicts the classical concept of precommitted identity of the premigratory crest, and the *Hox* code-default model as well.

Recent experiments have shown that not only the crest destined to the mandibular ectomesenchyme, but also the more rostral crest (premandibular crest) can generate the mandibular joint when transplanted to the second arch level, and absence of *Hox* expression was assumed to be sufficient for jaw patterning (Couly *et al.*, 1998). In this model, *Hox* gene regulation was still believed to be cell-autonomous. Trainor *et al.* (2002), however, found that it was the FGF8 secreted from the isthmus that downregulates *Hox* gene expression in the crest cells. According to these authors, Noden (1983) may have included *Fgf8*-expressing isthmus in the graft and non-*Hox*-expressing crest cells generated the mandibular joint at the hyoid arch level. Actually, by discarding the isthmic region from the rostral hindbrain graft, they were able to show that mandibular arch-specified crest transplanted to the hyoid level could give rise to a normal hyoid arch skeleton in the chimeric

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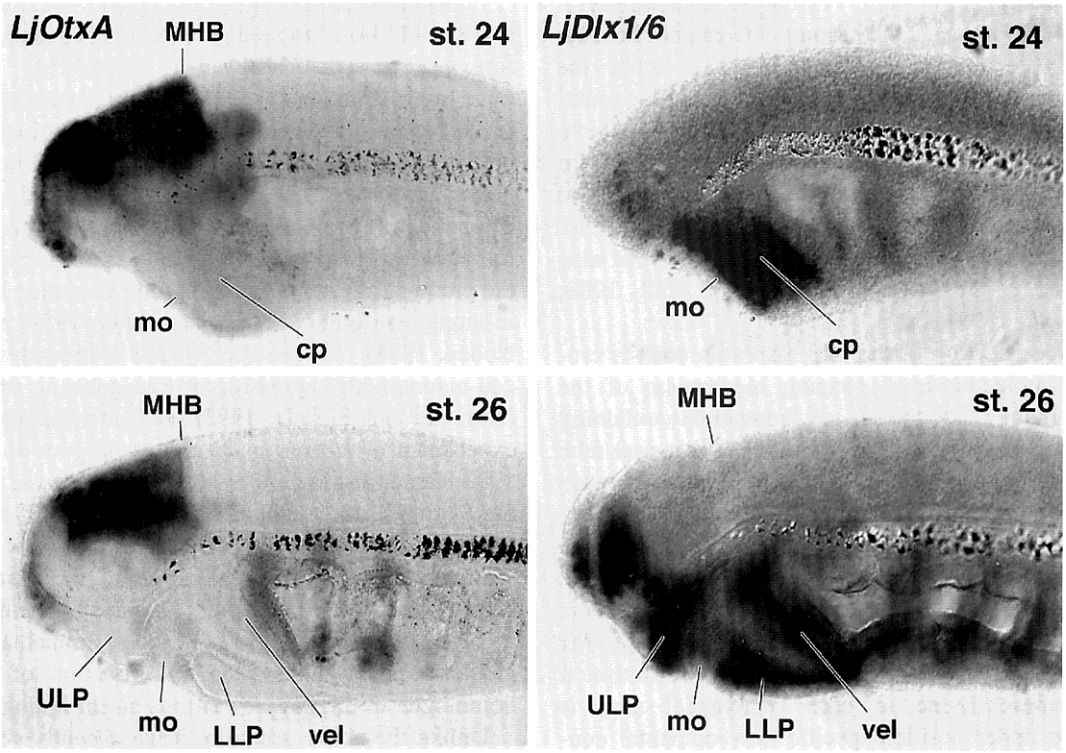


Figure 4. Expression patterns of jaw-patterning homeobox genes in lamprey embryos. Expression of *LjOtxA* (left; a possible cognate of gnathostome *Otx1* and *-2*) and *LjDlx1/6* (right; cognate of *Dlx1* and *-6*) are shown in two stages of lamprey embryos. *LjOtxA* has a clear expression boundary that corresponds to the mid-hindbrain boundary. At stage 24, this genes is slghtly expressed in the cheek-process ectomesenchyme. *LjDlx1/6* is expressed ubiquitously in the cheek process that later differentiates into upper and lower lips, as well as the velum. Although this expression pattern and sequence is reminiscent of the *Dlx1* expression in gnathostome mandibular-arch derivatives, the cheek process of the lamprey embryo is not directly equivalent to the mandibular arch in gnathostomes. Abbreviations: *cp*, cheek process; *LLP*, lower lip; *MHB*, mid-hindbrain boundary; *mo*, mouth; *ULP*, upper lip; *vel*, velum.

embryo. In the absence of FGF8, crest cells derived from the graft were induced to upregulate the normal *Hox* code through the interaction with the new embryonic environment. Since the homologue of *Fgf8* in the lamprey, *LjFgf8/17* is also expressed in the mid-hindbrain boundary in the lamprey (Murakami *et al.*, 2001), it is presumable that the mandibular arch ectomesenchyme in this animal is also devoid of *Hox* gene expression.

Another line of experimentation has shown that other regulatory genes are involved in the jaw patterning in gnathostomes. For example, in the *Hoxa2* mutant mouse, and also in the series transplantation experiments, duplicated elements were always the proximal portion of the mandibular arch skeleton, and the more rostral part could not be generated. A non-*Hox* homeobox gene, *Otx2*, may explain the patterning of the rest of the mandibular arch.

In gnathostomes, *Otx2* is developmentally expressed rostral to the mid-hindbrain boundary and also in the crest cells that originate from the same level (Figure 3; refs.; Osumi-Yamashita *et al.*, 1994; Köntges and Lumsden, 1996). Heterozygous mouse mutants of *Otx2* exhibited a graded series of phenotypes in the lower jaw, i.e., from an almost normal state to the total absence of the dentary (Matsuo *et al.*, 1995). The ear ossicles, malleus and incus (primary jaw joint of gnathostomes), were, however, always present. Interestingly, the latter skeletal elements correspond to those duplicated in the hyoid level of the *Hoxa2* deficient mouse. The patterning mechanism for the gnathostome mandibular arch thus appears to be a composite of the *Otx2*-dependent distal part and the proximal, articulating part which is more or less dependent on the absence of *Hox* expression (Mallo and Gridley, 1996; Couly *et al.*, 1998; reviewed by Kuratani *et al.*, 1998a).

The putative homologue of *Otx2* in the lamprey, *LjOtxA*, is also expressed rostral to the mid-hindbrain boundary and in the crest cells destined for the mandibular arch (Figure 4; Ueki *et al.*, 1998; Tomsa and Langelland, 1999). Apparently, lampreys have only one cognate for *Otx* genes, and another gene named *LjOtxB* (Ueki *et al.*, 1998) may possibly represent a cognate for gnathostome

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Otx5/Crx group (Germot *et al.*, 2001). Evolutionary duplication of *Otx* genes and correlated evolution of the neurosensory system in vertebrates has been summarized by Fritzsch *et al.* (2001).

In the lamprey embryo, midbrain-derived crest cells migrate into the cheek process, the putative homologue of the mandibular arch plus the first pharyngeal pouch (Damas, 1944; but see below). Here the homologous gene is expressed in an equivalent cell lineage found in the equivalent structural unit of the embryos. The same is true for the En-like protein expression in the mandibular arch muscle primordia (Holland *et al.*, 1993; but see Song and Boord, 1993; Hall, 1998; and Kuratani *et al.*, 2001 for the later development of the muscles). Thus, the similar expression patterns of regulatory genes and embryonic structural elements can be found in the oral region of the lamprey and gnathostomes in various aspects, and at this level, morphological as well as biological homologies can easily be established. Importantly, however, such a shared pattern will not explain the evolution of innovations. Instead, high levels of developmental constraint are expected in vertebrates. As far as the known developmental phenomena are concerned, the jaw-forming embryonic materials and responsible regulatory genes are all set up in the lamprey developmental system, and it is not the loss or change of any of those elements that can be associated with the specific absence of a jaw in the lamprey. If, however, the jaw is still truly an innovation of vertebrates, based on changes in the developmental program itself, it would rather be the usage of the genes and tissues that could explain the specific emergence of the jaw only in the lineage of gnathostomes. As discussed below, this expectation is actually plausible since the larval oral apparatus in the lamprey (upper and lower lips) is constructed in a totally different way from that for the upper and lower jaws of gnathostomes.

Comparative morphology

The upper lip of the ammocoete, or the large portion of the sucker in the adult, has often been equated to the maxillary part of the gnathostome jaw since, for example, Cuvier (1863), when it had not yet been realized that the ammocoete represented a larval form of the lamprey. Terminology of the trigeminal nerve branches reflect clearly that the upper lip was thought to be the origin of the upper jaw, and the velum as well as the lower lip, the lower jaw (Hatschek, 1892; Alcock, 1898; Johnston, 1905; Gaskell, 1908; but see Whiting, 1972, 1977). Detailed anatomy of the ammocoete oral region by Mallatt (1996) is also based on a similar comparison. However, this homology does not hold true for the embryonic developmental patterns of the two animal groups.

In gnathostomes, both the upper and lower jaws are direct derivatives of the mandibular arch. In the shark, for example, the mandibular arch of an early pharyngula resembles the more posterior pharyngeal arch, showing no dorsoventral differentiation (Goodrich, 1930; de Beer, 1937). The maxillary part of the jaw develops secondarily by growth of the dorsal part of this arch (Kuratani and Horigome, 2000; reviewed by Kuratani *et al.*, 2001). The ectomesenchyme in the mandibular arch is only a caudal part of the extensive trigeminal crest cells, the rostralmost ectomesenchyme in the head (Figure 2, below). The rostral half of this mesenchyme can be called the premandibular ectomesenchyme since it is found rostral to the mandibular domain. In a parallel fashion, the trigeminal nerve of a gnathostome can be divided into two portions; the ophthalmic nerve that innervates the premandibular (frontonasal) region of the head, and the maxillomandibular nerve for the mandibular arch derivatives. In the mapping experiments involving both avian chimeric embryos and vital dye labeling of amniote embryos, ectomesenchyme within the maxillary process was often erroneously mapped to the rostral midbrain of amniote embryos. However, these embryos are too young and the maxillary process has not yet formed. Shigetani *et al.* (2000) has shown that the maxillary process when it is clearly formed in the chick embryo, receives cells derived from the caudal half of the midbrain neural crest. Although there is no clear boundary to show the subdivisions within the trigeminal crest cell population (Kuratani, 1997; Graham, 2001), there seems little migration between the mandibular arch ectomesenchyme and the mesenchyme in the premandibular region as revealed by Shigetani *et al.* (2000).

In terms of comparative morphology, mandibular arch crest cells can be defined as the cell population that surrounds the mandibular mesodermal core, or the source of the trigeminal nerve-innervated muscles. As already discussed in the previous review (Kuratani *et al.*, 2001), the upper lip-forming crest cells in the lamprey do not surround the mandibular mesoderm, but the premandibular mesoderm, the direct derivative of the prechordal plate (reviewed by Kuratani *et al.*, 1999). Since the premandibular mesoderm secondarily arises from stage 21 of the lamprey (corresponding to the early pharyngula; Tahara, 1988), the cheek process can be equated with the mandibular arch and the first pharyngeal pouch before this stage, and later the process comes to include the premandibular region as well (Kuratani *et al.*, 1999, 2001). Therefore, although very similar functionally, the lamprey lips are derived from nonhomologous embryonic components as compared to the gnathostome jaws. Through morphological comparisons also, the strict homology between the lamprey lips and gnathostome jaws had already come into question (Starck,

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1979; Mallatt, 1996). Embryologically, the difference appears to be where the mouth should open, or where to differentiate protrusions using trigeminal crest cells. Also, if the homologous molecules are functioning in the development of jaws and lips, the evolutionary changes involved would be relevant to the difference in where to use the genes.

Epigenetics of jaw

Noteworthy in the hierarchical developmental process of the mandibular arch is the function of tissue interactions that lead to the localized expression of regulatory genes in the head. Importantly, the localized expression pattern of genes in the late pharyngula ectomesenchyme is not inherent to the premigratory crest cells, but is established by the topographical association of tissues. While the ectomesenchymal expression of these genes is autonomously regulated in the late pharyngula (Ferguson *et al.*, 2000), the initial regulation is primarily downstream of growth factor distribution. For example, in the chick and mouse embryos, epidermally derived growth factor FGF8 induces expression of its target gene, *Dlx1*, in the proximal ectomesenchyme, and similarly, distal ectoderm of the mandibular arch produces another growth factor, BMP4, which upregulates the downstream gene, *Msx1*, in the distal mesenchyme (Ericson *et al.*, 1998; Tucker *et al.*, 1998). Thus the local expression of ectomesenchymally regulated homeobox genes is involved in the specification of the mandibular region within the trigeminal crest cells at early stages (Trumpp *et al.*, 1999; Shigetani *et al.*, 2000), and in later development the same molecular cascades are functioning in proximo-distal (P-D) patterning of the mandibular arch itself (Neubüsser *et al.*, 1997; Thomas *et al.*, 2000). Although these molecular cascades are also apparent in the more caudal pharyngeal arches, their function seem to be suppressed partly due to the expression of *Hox* genes that is restricted caudal to the second arch (reviewed by Kuratani *et al.*, 1997). Actually, disruption of these ectomesenchymal genes in the mouse often lead to the phenotype restricted to the mandibular arch. In the lamprey, at least *LjDlx1/16*, the homologue of gnathostome *Dlx1*, is expressed in the nonhomologous ectomesenchyme in the lamprey as compared to gnathostomes since it is seen not only in the lower lip, but also in the upper lip mesenchyme (Figure 4; Myojin *et al.*, 2001). If the expression of the homologous gene has to be associated with an homologous embryonic element, we would expect that the gene would be expressed only in the velar and lower lip ectomesenchyme, as noted above.

In the above connection, Couly *et al.* (2002) have recently revealed that interaction between the head ectoderm and oral endoderm leads to the patterning of the upper and lower jaw in the chick. Probably through the function of a diffusible factor, sonic hedgehog, released from the rostral endoderm, the oropharyngeal membrane is defined early in development, which leads to the positioning and patterning of the jaws (Couly *et al.*, 2002). If the mouth is induced through the interaction between the ectoderm and endoderm, whether the position of the mouth opening is fixed in all the vertebrates or not should also be examined; if the lamprey upper lip involves a part of the premandibular ectomesenchyme, the lamprey mouth is thought to open relatively more rostral as compared to that of gnathostomes. In the amphioxus, the sister group of vertebrates, the mouth opens on the left side of the head and only secondarily does it acquire a symmetrical shape. Thus the mouth position may have been respecified within the lineage of vertebrates, and its position may have changed in the transition. In this sense, evolutionary comparison of the expression of *Fgf8* homologues would be very intriguing not only because this gene is known to be upstream of *Dlx1* in gnathostomes, but also its early expression domain is found lateral to the prospective mouth opening (stomodaeum) in the gnathostome embryo (Shigetani *et al.*, 2000).

Hypophysis, nasal placodes, trabecula and upper jaw

In addition to the possible difference in the position of the mouth, another obvious difference is found in the cranial ectoderm between the lamprey and gnathostomes, which would be inherently related to jaw evolution. Living agnathan embryos possess a single median placode named the nasohypophysial plate that differentiates into both the unpaired olfactory epithelium and hypophysis (Figure 5; Gorbman, 1983). This placode persists for a long time during development, providing an unusual pattern to the embryonic head of this animal. However, the single nostril, or the state of monorhiny (Janvier, 1993) appears to be a plesiomorphic character for vertebrates, and this difference is related to the development of the hypophysis.

In the gnathostome, the hypophysis arises as a part of the oral ectoderm, whereas in agnathans, the hypophysis lies rostral to the oral ectoderm, as a part of the cephalic surface ectoderm (Figure 5). As noted by Janvier (1996, 2001), the state of paired nostril (= diplorhiny) is an apomorphic trait for gnathostomes, and it is likely that there were a number of variations in cranial ectodermal patterning in the early phases of their evolution.

In gnathostomes also, nasal placodes and anlage of adenohypophysis (Rathke's pouch) are developmentally coupled in various aspects. As exemplified in the chick and amphibian development, ectodermal parts destined to

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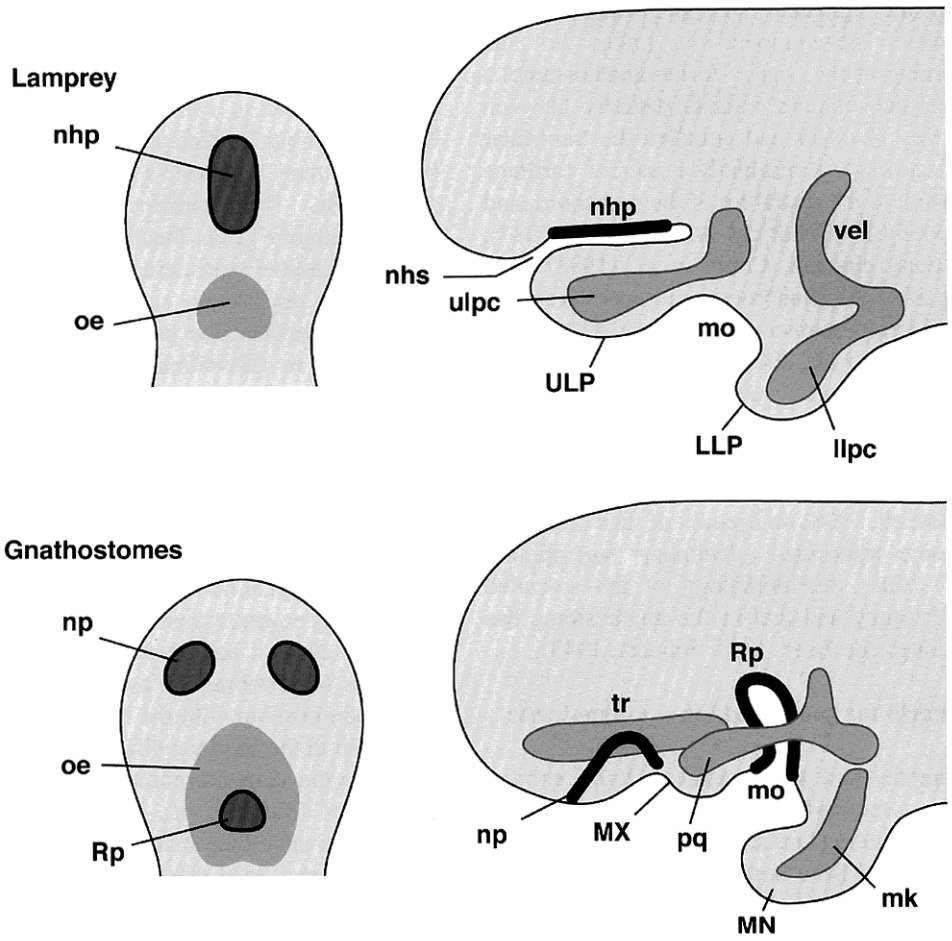


Figure 5. Rearrangement of the ectomesenchyme and jaw evolution. Early specification of the head ectoderm (left) and late patterning of the chondrogenic ectomesenchyme (right) are compared between the lamprey (top) and gnathostome (bottom) embryos. In the lamprey, nasal epithelium and adenohypophysis arise from a single common anlage, the nasohypophysial plate, whereas in gnathostomes, they have separate placodes. Note that the gnathostome hypophysis arises as a part of the oral ectoderm. This difference in ectodermal specification correlates with the distribution and patterning of the chondrogenic ectomesenchyme in the two animal groups. Namely, the mandibular ectomesenchyme in the lamprey stays within the velar and lower lip regions, while in gnathostomes, the equivalent cell population can grow dorsorostrally to form the upper jaw skeletal elements. Similarity between the lamprey upper lip and gnathostome upper jaw is superficial and the cartilages in these structures occupy nonidentical positions with respect to the oral ectoderm and hypophysis. Abbreviations: *LLP*, lower lip; *llpc*, lower lip cartilage; *mk*, Meckel's cartilage; *MN*, mandibular process; *mo*, mouth; *MX*, maxillary process; *nhp*, nasohypophysial plate; *nhs*, nasohypophysial sinus; *np*, nasal placode; *oe*, oral ectoderm; *pq*, palatoquadrate; *Rp*, Rathke's pouch; *tr*, gnathostome trabecula; *ULP*, upper lip; *ulpc*, upper lip cartilage; *vel*, velar cartilage.

these placodes are closely mapped in the head at the early neurula stage (Couly and Le Douarin, 1985, 1990). Such a mapping, however, does not necessarily indicate the state of committment for these organs, but inductive events take place later in development. In the chick embryo, the ventral diencephalon induces part of the underlying oral ectoderm to differentiate into the adenohypophysis (Gleibermn *et al.*, 1999). Induction of the nasal placodes, on the other hand, is not well understood. Although nothing is known about the developmental induction of these organs in the lamprey, both the nasal and hypophysial placodes are attached to the comparable parts of the embryonic brain, implying that the conserved molecular cascades are functioning in inducing these placodes, in nonidentical ectodermal parts (Figure 5; Murakami *et al.*, 2001).

Importantly, the space between the separated hypophysis and paired nasal placodes is the site of chondrification for trabecular and maxillary cartilages in gnathostomes. The above-noted difference in the topography between the oral ectoderm, hypophysis, and nasal placodes between gnathostomes and agnathans might possibly provide the basis for morphological differences in mesenchymal com-

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ponents between the agnathan and gnathostome head; craniofacial skeletal development is linked to the ectodermal patterning of the head. In the gnathostome, a part of the prechordal cranium extends rostrally between the pair of olfactory placodes and is called the trabecular cartilage. This cartilage is originally a pair of cartilage rods that arise rostral to the rostral tip of the notochord, and lateral to the hypophysis (Goodrich, 1930; de Beer, 1937). By using chick-quail chimera, Couly *et al.* (1993) have shown that this part of the chondrocranium arises from the neural crest-derived ectomesenchyme. As noted in a previous review (Kuratani *et al.*, 2001), the trabecula-forming ectomesenchyme in the shark occupies an identical position to the upper lip-forming ectomesenchyme of the lamprey. A pair of cartilage rods have long been recognized below the brain of the lamprey and called trabecular cartilages (Shipley 1887; Gaskell, 1908) on account of their similarity to the gnathostome trabecula. Including our opinion (Kuratani *et al.*, 2001), the homology of the so-called trabecula in the lamprey and that in the gnathostome has often been questioned (de Beer, 1937; Johnels, 1948).

Evo-Devo scenario for jaw evolution – a hypothesis

Both in the lamprey and gnathostomes, *Dlx1/6* expression appears to be associated with perioral structures with apparently similar function (Janvier, 1993). However, this oral apparatus is formed from both the premandibular and mandibular ectomesenchyme in the lamprey, whereas in gnathostomes, it is patterned from the mandibular ectomesenchyme only. Interestingly, the suprarostral cartilage in the tadpole larvae of the frog appears to be derived from the premandibular ectomesenchyme, thus resembling temporally the patterning of the oral region of the lamprey larva. Incidentally, Huxley (1876) tried to equate the tadpole and ammocoete oral anatomy, which turned out to be partly correct embryologically. To this, Balfour (1881) alluded a possibility that the jawless vertebrate ancestor might have possessed a suctorial mouth like the lamprey's, which was recapitulated in the development of the frog. Absence of such a stage in shark development was explained as due to the abbreviated development of this animal. Also, premandibular and mandibular origins of the ammocoete lips are reminiscent of the vertebrate archetype postulated by Richard Owen (1866), in which upper and lower jaws are assumed to be derived from the rostral two pharyngeal-arch skeletal elements. As discussed above, such a formulation is more suitable for the ammocoete larvae rather than for gnathostomes.

In the comparison of the lamprey lips and gnathostome jaws, we have seen a situation in which homologies seen in gene expression patterns, embryonic units, and functional similarity do not coincide with each other. Therefore, there is a chance that the gnathostome jaw was brought about not simply by mandibular-arch transformation (adaptation), but rather that ancestral constraints in development were overcome to establish an entirely new pattern of ectomesenchymal differentiation. In this regard, the vertebrate jaw may represent a true evolutionary novelty in a strict sense. There are a number of examples in which nonhomologous genes function in the same developmental aspects of homologous structures (reviewed by Hall, 1994; 1998). In the present case, however, the morphological homology between the jaws and lips was denied morphologically. In this connection, the lamprey trabecula is more likely to represent an anteriorly elongated parachordal cartilage, rather than the gnathostome trabecula (Johnels, 1948; reviwed by Kuratani *et al.*, 2001).

The homeobox gene specific to the oral ectomesenchyme (*Dlx1* cognates) is expressed in different sets of craniofacial ectomesenchyme in the lamprey and gnathostome. Could the morphological homology of the oral apparatus be represented by gene expression as in the vertebral homology? In the latter case, it has been found that axial level-specific identities of vertebrae are associated not with the numbering of somites, but with the homologous sets of *Hox* genes expressed in the somites; different numbers of vertebrae are found for the same morphological identity in each group of vertebrates (Burke *et al.*, 1995; Cohn and Tickle, 1999). It is conceivable then that the regulation of the *Hox* genes along the axial level was flexible, but morphological identities of bones were stable in the developmental program downstream of the *Hox* code. In the jaw evolution, the suggested shift of gene expression does not seem to be simple. If we are to suggest that the jaw was obtained by evolutionary homeotic transformation along the axis of the pharynx, we will have to assume that the premandibular region represents another pharyngeal arch rostral to the mandibular arch, as transcendental comparative morphology used to conclude (Huxley, 1874; see de Beer, 1937; reviewed by Kuratani *et al.*, 1998a). Similarly, the trabecular cartilage would represent another pharyngeal-arch cartilage (Huxley, 1876; reviewed by Goodrich, 1930; and by de Beer, 1937). Unlike the serially identical developmental mechanism in vertebral patterning (differentiation and histogenesis of somites), however, the developmental mechanism of nasofrontal-pharyngeal regions differs conspicuously from each other in terms of the skeletal patterning as reviewed above and in association with the central and peripheral nervous systems (reviewed by Graham, 2001).

In conclusion, thus far recognized developmental elements including the various cell populations, regulatory genes, as well as overall phylotypic embryonic morphology, are conserved between the lamprey and gnathostomes. However, the usage of genes (in which part of the

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ectomesenchyme regulates the genes) slightly differs between the two animal groups, and this small change may possibly be crucial for the gnathostome-specific patterning of the oral ectomesenchyme in which both the upper and lower jaws are derived only from the mandibular arch (Figure 5; Kuratani *et al.*, 2001). It may possibly be the epigenetic interactions of tissues that is the basis of both the constrained and changed developmental pattern, and this appears to be the only way to reconcile the apparently inconsistent homology of genes and morphological homology.

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