

Pattern formation in the urodele mechanoreceptive lateral line: what features can be exploited for the study of development and evolution?

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ABSTRACT The lateral line is a specialized system of mechano- and electrosensory organs found in anamniotes. This system develops from ectodermal placodes, which migrate extensively along specific routes and deposit sensory organ anlagen at regular intervals, making it ideal for examining several important aspects of pattern formation. Urodele embryos are excellent model organisms for studies of pattern formation in the lateral-line system. The results of such studies are also important for understanding the evolutionary control of changes in pattern. The developmental mechanisms which control pattern formation in the urodele lateral line are reviewed, and some of the broader evolutionary implications of these mechanisms are discussed.

KEY WORDS: *lateral-line system, neuromast, pattern formation, evolution, Ambystoma mexicanum*

Introduction

Although present only in lower vertebrates, the lateral-line system is studied in a variety of biological disciplines, including sensory and neurophysiology (Dijkgraaf, 1962; Bodznick, 1989), regeneration (Corwin *et al.*, 1989), and evolution (Jorgensen, 1989; Kalmijn, 1989), as well as embryonic development (Lannoo and Smith, 1989). The lateral line of urodeles is particularly amenable to experimentation since sensory organs are on the body surface and thus easily accessible, electroreceptors are present, the hair cells are capable of regeneration, and the development of the system has been extensively described (for review see Lannoo and Smith, 1989).

Morphology of the lateral line system

The lateral line is a specialized sensory system of fish and aquatic amphibians. The system contains two major types of sensory organs, consisting of electroreceptive ampullary organs (which detect weak electrical currents in the water) and mechanoreceptive neuromasts (which detect water displacements).

Among amphibians, ampullary organs are found only in caecilians (legless salamanders) and on the heads of urodeles (Fritzsche and Münz, 1986). Although believed to be evolutionarily derived from neuromasts, innervated by the same nerves, and placodal in origin, little is known about their embryonic origin and patterning (see Northcutt *et al.*, 1994, 1995).

The development of the neuromast system has been more

extensively studied. Neuromasts are composed of clusters of mechanoreceptive hair cells surrounded by support cells and covered with a gelatinous cupula (Fig. 1). Each hair cell is morphologically and functionally polarized. Within each neuromast, the hair cells are arranged to be maximally receptive along the long axis of the organ, imparting a morphological and functional polarity to the organ. Neuromasts are organized into several distinct lines on the head, body and tail, each of which has neuromasts of different specific polarities to permit detection of water movement in all directions (Fig. 2).

Development of the mechanoreceptive lateral line

The lateral-line system develops from two or more ectodermal thickenings (placodes) similar to those which form the lens, otic and nasal vesicles. Lateral-line placodes arise by delamination of ectoderm near the cranial neural folds, rostral and caudal to the otic vesicle (see Webb and Noden, 1993, for review). Although there are six major (and a few minor) lines in ambystomatids, there is some uncertainty over the exact number of lateral-line placodes in urodeles. Estimates range from two to eight (see Northcutt *et al.*, 1994).

Abbreviations used in this paper: c, cupula of neuromast; DL, dorsal body lateral line; IO, infraorbital (head) lateral line; k, kinocilium of hair cell; ML, middle (main) body lateral line; MN, mandibular (head) lateral line; n, nerve; NCD, neural crest-deficient; s, stereovilli (stereocilia) of hair cell; sc, support cell(s) of neuromast; SO, supraorbital (head) lateral line; VL, ventral body lateral line.

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However, the positions of the lateral-line ganglia and the pattern of innervation (Northcutt, 1992b) suggest that all neuromast lines may arise from 2-3 precursor placodes which subsequently split (Fig. 3). Much of the controversy may arise from examining embryos at different stages using different techniques. If this hypothesis is correct, the number of placodes would appear greater at later stages.

At stage 35 (Bordzilovskaya *et al.*, 1989) in the axolotl, the distal half of lateral-line placodes form primordia which, on the trunk, migrate along specific pathways depositing neuromast anlagen at regular intervals (Smith *et al.*, 1988; Lannoo and Smith, 1989) (for purposes of this discussion, "distal" refers to the rostral portion of the placodes which form the head lines, and the caudal portion of those which form the trunk lines). The nerves which supply the system arise from the proximal half of the same placodes. Neurites are inserted into the migrating primordia (Fig. 4), an interesting, and perhaps unique, example of neurites elongating to accompany the migration of their target organs.

These characteristics make the mechanosensory lateral line ideal for examining the mechanisms which control such developmental phenomena as the guidance of cell migration, pattern formation (of a regularly-spaced array of sensory organs), the origin of polarity (of both the sensory organs and the placodes themselves), and neurite outgrowth and targeting.

Cranial/trunk dichotomy in lateral-line primordia

There are several distinct differences in the development of head and trunk neuromast lines in urodeles (Graveson *et al.*, submitted). Placodes which form head lines, rather than migrating, elongate into broad "sensory ridges", which separate into neuromast anlagen (Winklbaauer and Hausen, 1983; Northcutt *et al.*, 1994). Trunk primordia are more cohesive and undergo a true migration (Smith *et al.*, 1990; Northcutt *et al.*, 1994; see Fig. 4). Primordia on the trunk produce neuromasts with a single polarity,

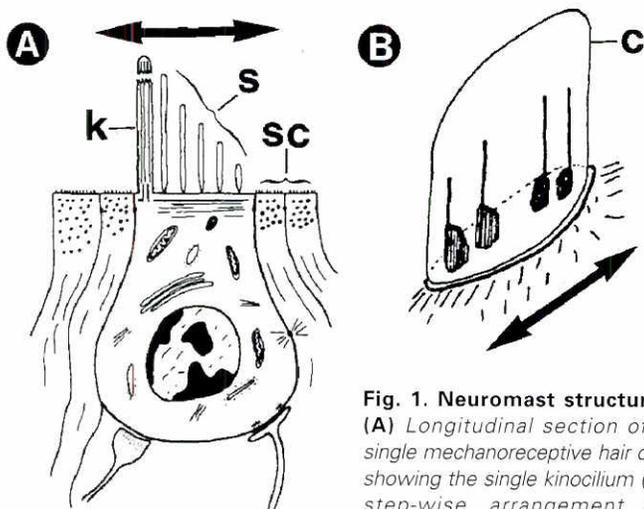


Fig. 1. Neuromast structure. (A) Longitudinal section of a single mechanoreceptive hair cell showing the single kinocilium (k), step-wise arrangement of stereovilli (stereocilia; s), and surrounding support cells (sc). This cell would be maximally sensitive to movement in the plane of the paper (arrow; see Flock, 1967). (B) Arrangement of hair cells along the long axis of a neuromast, with the kinocilia at opposite poles, imparting a maximal sensitivity parallel to the long axis (arrow). C, gelatinous cupula covering the organ. (After Lannoo and Smith, 1989).

while those on the head form lines composed of orthogonal couplets of opposite polarities (Lannoo, 1987a; Lannoo and Smith, 1989). In urodeles, head primordia form ampullary organs, whereas trunk primordia do not (Northcutt *et al.*, 1994, 1995). Neural crest cells are required for the trunk primordia to deposit neuromast anlagen, but not for sensory organ deposition on the head (Graveson *et al.*, submitted). For these reasons, it is imperative to know whether any aspect of neuromast patterning is specific to head and/or trunk lines.

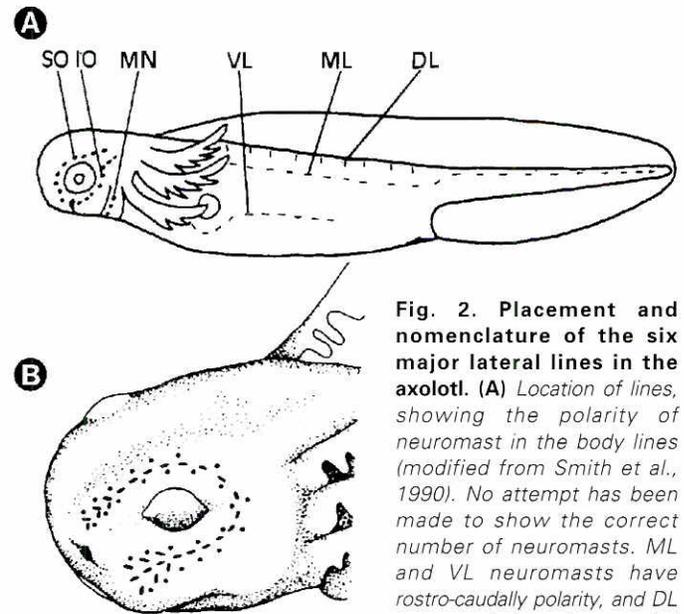


Fig. 2. Placement and nomenclature of the six major lateral lines in the axolotl. (A) Location of lines, showing the polarity of neuromast in the body lines (modified from Smith *et al.*, 1990). No attempt has been made to show the correct number of neuromasts. ML and VL neuromasts have rostro-caudally polarity, and DL neuromasts have dorso-ventral polarity. Nomenclature is per Smith *et al.* (1988); Northcutt (1992b) notes additional minor lines on the head, and further subdivides the MN. (B) SO and IO lines, showing the orthogonal polarities of neuromasts within single head lines, and the peripheral placement of ampullary organs (solid circles). (From Lannoo and Smith, 1989).

Evolutionary and phylogenetic significance

Evolutionary and phylogenetic significance

Studies of lateral-line development may also have significant evolutionary implications. The lateral line is considered a primitive vertebrate sensory system which has undergone little derivation. Indeed, modifications of the basic hair cell may have given rise to many vertebrate special sense receptors (Northcutt and Gans, 1983; Jorgensen, 1989). Neuromast hair cells are still very similar to those of the inner ear (Platt *et al.*, 1989). Furthermore, variations in lateral line sensory organ pattern are often important characteristics for determining phylogenetic relationships among lower vertebrates (Lannoo, 1987a,b; Northcutt, 1989; Webb, 1989a). Therefore, an understanding of the developmental mechanisms which control neuromast patterning may contribute to an understanding of how these mechanisms could be modified to bring about evolutionary diversification of sensory organ pattern.

As well, like the lens, ear, and nose, the lateral line system is placodal. Ectodermal placodes and neural crest cells are key evolutionary innovations of vertebrates, which together are almost exclusively responsible for the formation of the vertebrate head

(Northcutt and Gans, 1983). It has also been proposed that neuromasts induce dermal bone formation by neural crest cells (Merrillees, 1975), which suggests that the lateral line may have been responsible for the evolution of dermal bone (Moy-Thomas, 1938; Northcutt and Gans, 1983; Meinke, 1986). As well, the lateral-line system may have played an important role in the evolution of pigment cell patterns (Parichy, 1996a,b).

Neural crest and placodal cells also share many characteristics. In their seminal analysis, Northcutt and Gans (1983) noted that both are migratory ectodermal derivatives and form similar sensory/neural tissues. Recently it has been reported that placodes (like neural crest) have the potential to form ectomesenchyme (Kirby, 1988) and neural crest cells (like placodes) can form neuromasts (Collazo *et al.*, 1994). The cranial/trunk dichotomy in lateral-line placodes resembles that of neural crest. These observations suggest an even closer relationship between neural crest and placodal ectoderm than previously suspected, and strongly supports the contention that these two key vertebrate tissues arose from a common precursor (Northcutt and Gans, 1983).

Therefore, studies of the developmental interactions between lateral line elements and neural crest cells may prove crucial for understanding the evolution of these key vertebrate tissues. Indeed, the mechanosensory lateral line could prove an ideal model for the emerging science of evolutionary developmental biology (see Hall, 1992; Northcutt, 1992a).

Developmental control of neuromast patterning

The developmental mechanisms which control neuromast patterning are likely different in the head and the trunk. Little is known about the complex patterning of neuromasts on the head (but see Winklbauer and Hausen, 1985). Therefore, I shall concentrate on the mechanisms which regulate lateral-line development on the trunk.

Embryos of the axolotl (*Ambystoma mexicanum*) are ideally suited to such studies. Their large size and relatively slow development greatly facilitate experimental manipulations. The availability of color variants, particularly albino (*a/a*) and melanoid (*m/m*), is also useful. Migrating cells can easily be observed, *in vivo*, following transplantations of pigmented wild-type tissues into albino embryos. Maternal pigment is a non-toxic and homospecific marker that does not suffer from the disadvantages of many chemical or interspecific markers. Results may still be affected by surgical trauma, and the maternal pigment eventually fades into invisibility. The former problem can be minimized by the use of appropriate controls. Fading cannot be circumvented, but can be delayed by using heavily-pigmented donors, such as those from *m/m* mothers.

The axolotl also has the basic urodele advantages of having the neuromasts on the body surface and not in canals (as in fish), and having electroreceptors on the head (unlike anurans, which have none). The axolotl is also neotenic and therefore does not lose or cover its sensory organs at metamorphosis, as do some terrestrial anurans and urodeles (Fritsch, 1990).

Neuromast patterning on the trunk of axolotl embryos is controlled by the coordinated efforts of at least three different tissues: the substrate through which the primordium migrates, neural crest cells, and the primordium itself.

What is the role of the substrate?

In early studies on the development of the lateral line, Stone (1933) concluded that "... there is nothing in the future pathway of a migrating lateral-line primordium to predetermine the position of a sense organ...". Since then, Smith *et al.* (1990) have re-examined this conclusion by surgically manipulating the ectoderm in the path of migrating ML primordia.

In sham operations, where ectoderm was lifted and immediately replaced in the same orientation, migration of the primordia continued through the area, and neuromast anlagen were deposited without interruption. When ectoderm was rotated 180°, migration and sensory organ deposition was similarly unaffected.

However, when ectoderm was rotated 90°, the change in ectodermal polarity caused all ML primordia to either stop migrating completely, or change direction at the rostral edge of the graft. Furthermore, diverted primordia wandered, apparently aimlessly, unless the pathway of another line was encountered, whereupon they could follow the new pathway in either direction. Diverted primordia deposited neuromasts ectopically, but such neuromasts did not have the expected rostro-caudal polarity of ML neuromasts. However, all maintained the same polarity with respect to the direction of migration of the primordium (Fig. 5).

Smith *et al.* (1990) concluded that the substrate through which trunk lateral-line primordia migrate has "tracks" which guide migration, most likely through contact guidance. Thus, the

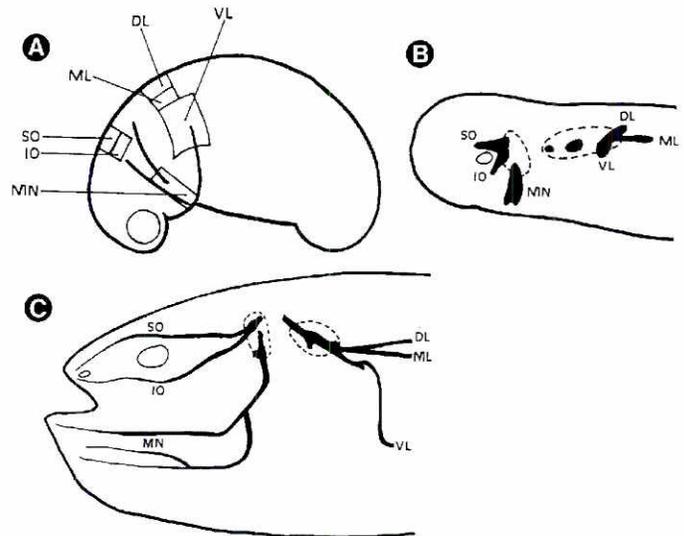


Fig. 3. Location of lateral-line placodes. (A) Locations in stage 26 axolotl embryo, as determined by transplanting pigmented ectoderm into albino embryos (Smith *et al.*, 1988). (B) Locations of placodes in stage 35 embryos, as observed with ectodermal staining (after Northcutt *et al.*, 1994). (C) Approximate locations of lateral-line nerves, showing common roots (after Northcutt, 1992b). From the placement of nerves (C) and divergence of placodes (B), all lines could arise from 2 large placodes (one for head lines, one for body) in approximately the areas enclosed by broken lines. This would roughly correspond to the SO/IO and DL/ML/upper VL areas in (A), and would imply that placodes were partitioned by surgery. However, the presence of pigmented cells from transplants in, particularly, the MN area in younger embryos (A), suggests that there may be later recruitment of ectodermal cells by some primordia.

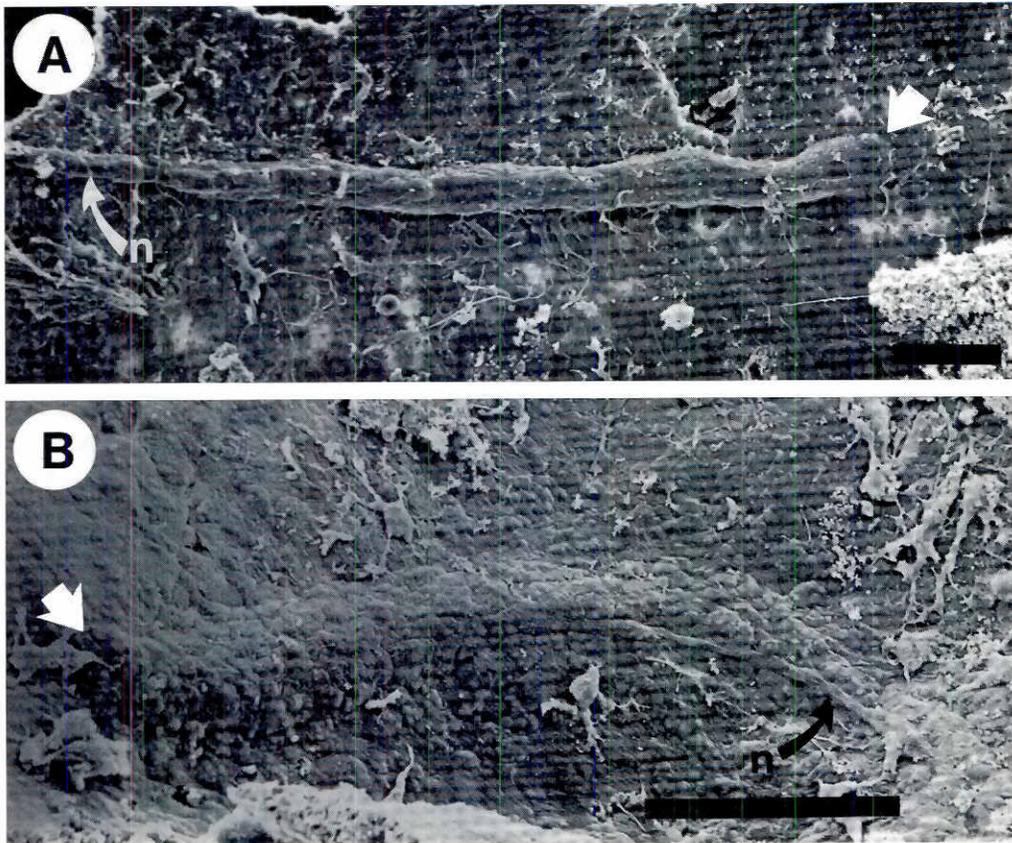


Fig. 4. Scanning electron micrographs of lateral-line primordia on the underside of the ectoderm of stage 36 embryos, showing nerves (n) inserted into them. The distal ends are indicated with arrows. (A) Migrating ML primordium, with compact elongated morphology typical of body primordia. (B) Elongating SO primordium, showing the broader "sensory ridge" typical of head lines. Bars, 100 μ m. (From Smith *et al.*, 1990).

substrate (either ectoderm or the underlying extracellular matrix) determines the location of neuromast lines on the body. Furthermore, since diverted primordia continue to migrate, the motive force for migration cannot be a property of the substrate tracks, but has to be due to the primordium itself. Similarly, neuromast polarity is an inherent property of the primordia, but only relative to the direction of migration, which is determined by the substrate.

What is the role of neural crest cells?

Although neural crest cells have frequently been hypothesized to be involved in the development of the lateral-line system, their role had not been systematically examined until recently. In one study, the development of ML neuromasts was examined in the *p* mutation of the axolotl. This single gene mutation specifically affects the development of a subpopulation of neural crest cells (Graveson and Armstrong, 1990, 1994, 1996). This mutation also affects both the migration of ML primordia and neuromast differentiation (Smith *et al.*, 1994). Perhaps surprisingly, these effects were not due to the presence of mutant neural crest cells, but to a direct effect on this placodal derivative.

In a second study (Graveson *et al.*, submitted) neural crest cells of wild-type embryos were excised from specific regions prior to their emigration from the neural tube, and the effects on ML development were examined. Extirpations of neural crest from immediately dorsal to the placodal ectoderm did not affect formation or migration of lateral-line primordia, or deposition of neuromasts. Similarly, extirpation of cranial neural crest did not affect the development of head lines. When regions of neural crest

were excised from the trunk, primordia migrated normally through the NCD region. However, although neuromasts were deposited both rostral and caudal to the NCD area, none were deposited in it, leaving a neuromast-free region (Fig. 6).

Based on these results, Graveson *et al.* (submitted) concluded that neural crest cells neither induce nor trigger the migration of lateral-line placodes. In addition, cranial neural crest cells do not appear to be involved in neuromast patterning on the head. Neither can they establish substrate tracks on the trunk, since migration through NCD areas is normal. However, trunk neural crest cells do play a definite role in patterning neuromasts on the body, but do not specify neuromast placement or spacing, since neuromast anlagen can be deposited in ectopic locations by diverted primordia. The role of trunk neural crest cells is more likely permissive, and perhaps due to some modification the sub-ectodermal space (Graveson *et al.*, submitted).

What is the role of the primordium?

Lateral-line primordia provide the motive force for migration, and appear to play a key role in determining neuromast polarity. However, little direct work has been done on the function of the primordium in lateral line patterning. We have recently begun such an examination.

When developing lateralis nerves were severed rostral to the ML primordia just after the beginning of their migration (stage 35-36 in the axolotl; see Smith *et al.*, 1988), migration and deposition of neuromast anlagen continued uninterrupted (unpublished observation). Thus, insertion of neurites into the primordium is unnecessary for primary neuromast patterning, although

innervation may later become necessary to prevent degeneration of the sensory organs (Brockelbank, 1925).

When the proximal (rostral) halves of migrating ML primordia were excised soon after the initiation of migration (stage 35-36), migration of the remaining portions of the primordia continued normally. However, neuromast anlagen were not deposited immediately after the site of partitioning. Only after the partial primordia had migrated some distance did neuromast deposition resume. In each case the partial line formed corresponded to the portion of the primordium which remained, whereas the gap in the line corresponded to the portion removed (unpublished observations).

This suggests a pre-existing, linear pattern of neuromast anlagen within the migrating primordium, that sensory anlagen are deposited in order from the proximal (rostral) end of trunk primordia, and that body primordia are incapable of regenerating missing portions. Interestingly, these results are identical to those observed following removal of portions of the SO line on the head of *Xenopus* (Winklbauer and Hausen, 1985). Therefore, a linear pre-pattern of neuromast anlagen is probably one feature common to both head and body primordia.

Discussion

Pattern formation in the trunk lateral-line system clearly results from of multi-level, coordinated control by several tissues. Substrate tracks guide the migrating primordia and control the locations of the lines. Although their exact function is still uncertain, neural crest cells permit deposition of sensory organ anlagen. Finally, the primordia are actively migratory, contain a linear pre-pattern of neuromast anlagen, and contain information on the polarity of the neuromasts they deposit. However, neuromast polarity is not relative to the axis of the embryo, but rather to the direction of migration, and is therefore indirectly determined by substrate tracks.

What are some future directions for developmental studies?

Much remains to be done before the mechanisms which control patterning in the lateral-line system are fully defined. Of paramount importance is ascertaining the biochemical nature of the substrate tracks,

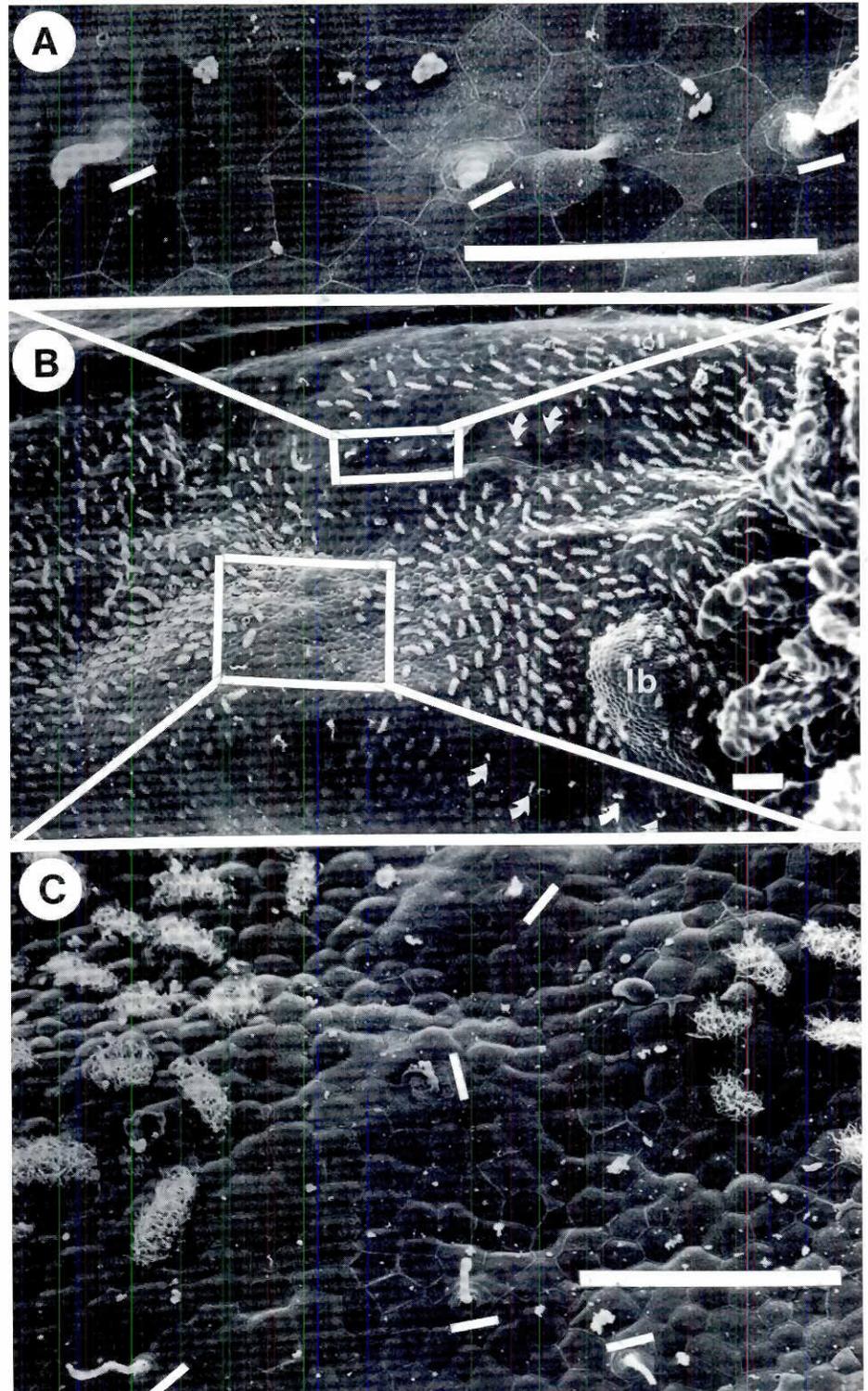


Fig. 5. Scanning electron micrographs of the right side of an axolotl hatchling, showing the location (arrows in B) and polarity (A,C) of neuromasts deposited by a diverted ML primordium. (A) Prior to being diverted, neuromasts have the rostral-caudal polarity typical of the ML. (C) Where the primordium migrated ventrally, the neuromasts have a dorso-ventral polarity. Short bars show the polarity of the adjacent neuromasts. Bars, 100 μ m. (From Smith et al., 1990).

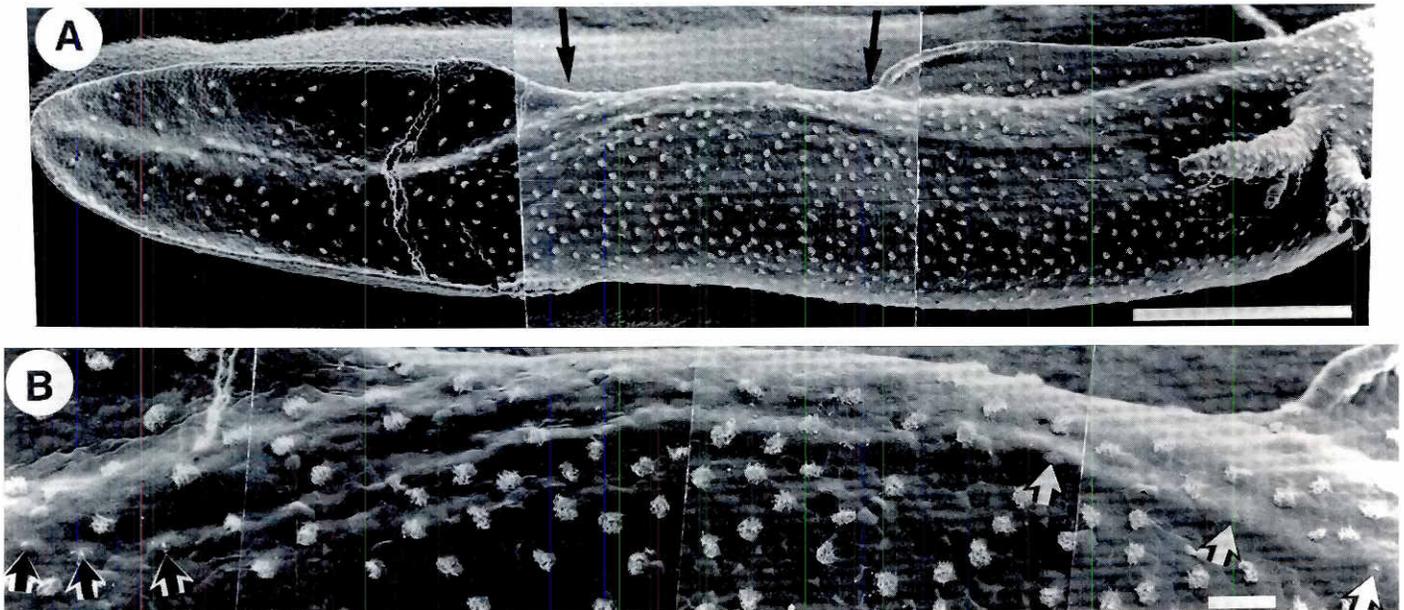


Fig. 6. Effect of neural crest on neuromast deposition in the trunk. (A) Scanning electron micrograph of an embryo from which a section of trunk neural crest was removed (between arrows). (B) Higher magnification of the NCD area in (A), showing erupted ML neuromasts rostral and caudal to, but not in, the NCD area. Bars: A, 1 mm; B, 100 μ m. (From Graveson *et al.*, submitted).

determining how they are established, and elucidating the exact role of trunk neural crest cells in controlling neuromast deposition.

How neuromast spacing is determined needs to be known. Smith *et al.* (1988, 1990) speculated that each neuromast anlagen, once deposited, establishes an inhibitory field which prevents the deposition of other anlagen. However, this is based solely on an observed inhibitory effect of newly-erupted neuromasts on surrounding ciliated epithelial cells and needs to be critically tested. An alternative suggestion is that spacing is determined by the subjacent myomeres in teleosts (Webb, 1989b). This is unlikely unless spacing mechanisms are radically different in teleosts and urodele amphibians, since neuromasts can be deposited ectopically along a single myomere by diverted primordia (Fig. 5).

How the pre-pattern within the primordia is established prior to migration, and how placodes are initially induced from head ectoderm are not yet understood (although Smith *et al.*, 1994 have proposed that they arise as a direct or indirect result of neural induction). How lateral-line placodes, once formed, are partitioned into proximal (neurogenic) and distal (sensory organ-producing) portions also remains unknown.

What are the evolutionary implications of the developmental studies?

Some conclusions such as the following regarding evolutionary divergence in lateral line pattern can be drawn from current knowledge: since substrate tracks govern the position of lines on the body, shifts in the location of tracks could ultimately be responsible for differences in the location of lines in different organisms. Changes in neuromast polarity could reflect changes in the primordia themselves, perhaps in conjunction with changes in track location. Similarly, gaps in a line could reflect changes in either the primordia (which have "lost" portions) or the ability of

neural crest cells to permit neuromast deposition within specific areas. Complete loss of sensory lines may reflect partial or complete loss of placodes as, for example, in amniotes. Intermediate cases of this phenomenon may be present in organisms which retain lateralis nerves without sensory organs. Alternatively, there may be organisms in which sensory organs develop without innervation and subsequently degenerate.

Clearly, further study of the developmental control of pattern formation in the lateral-line system may prove invaluable for elucidating the mechanisms responsible for evolutionary changes in lateral line pattern.

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