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Origin of the vertebrate inner ear: evolution and induction of the otic placode

ANDREA STREIT

Department of Craniofacial Development, King's College London, UK

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ABSTRACT

The vertebrate inner ear forms a highly complex sensory structure responsible for the detection of sound and balance. Some new aspects on the evolutionary and developmental origin of the inner ear are summarised here. Recent molecular data have challenged the longstanding view that special sense organs such as the inner ear have evolved with the appearance of vertebrates. In addition, it has remained unclear whether the ear originally arose through a modification of the amphibian mechanosensory lateral line system or whether both evolved independently. A comparison of the developmental mechanisms giving rise to both sensory systems in different species should help to clarify some of these controversies. During embryonic development, the inner ear arises from a simple epithelium adjacent to the hindbrain, the otic placode, that is specified through inductive interactions with surrounding tissues. This review summarises the embryological evidence showing that the induction of the otic placode is a multistep process which requires sequential interaction of different tissues with the future otic ectoderm and the recent progress that has been made to identify some of the molecular players involved. Finally, the hypothesis is discussed that induction of all sensory placodes initially shares a common molecular pathway, which may have been responsible to generate an 'ancestral placode' during evolution.

Key words: Chordates; sensory placode; placode field.

INTRODUCTION

Paired special sense organs of the head, cranial sensory ganglia and migratory neural crest cells are thought to be vertebrate specific innovations during evolution (Northcutt & Gans, 1983; Butler, 2000; Shimeld & Holland, 2000). Of the sensory organs, the vertebrate inner ear is responsible for the detection of sound, balance and acceleration. In the adult, it forms an elaborate structure with multiple sensory patches containing mechanosensory hair cells transmitting auditory and balance information, mineralised otoliths and supporting cells all arranged in a highly organised pattern (Torres & Giraldez, 1998; Baker & Bronner-Fraser, 2001). Despite this complexity the entire inner ear arises from a simple epithelium adjacent to the hindbrain, the otic placode, which is thought to be specified through inductive interactions with surrounding tissues. The otic placode invaginates, neuroblasts delaminate from its ventromedial part to generate the cochlear-vestibular ganglion and the otic vesicle separates from the surface ectoderm. In a series of morphogenetic events the vesicle generates the elaborate architecture of the inner ear: the vestibular part consisting of 3 semicircular canals with associated cristae, and of the sacculus and utriculus containing the otolith organs and the auditory part formed by the cochlear duct lined by the sensory cells. Could an analysis of developmental mechanisms contribute to our understanding of how the inner ear evolved and vice versa? This review discusses the evolutionary origin of the vertebrate inner ear and summarises our current knowledge about the mechanisms that regulate the induction of the otic placode.

EVOLUTION OF THE VERTEBRATE INNER EAR

A longstanding view holds that migratory neural crest cells and sensory placodes (which contribute to the paired cranial sense organs) are vertebrate specific acquisitions not found in nonvertebrate chordates

Correspondence to Dr Andrea Streit, Department of Craniofacial Development, King's College London, Guy's Campus, London SE1 9RT. e-mail: andrea.streit@kcl.ac.uk

(Northcutt & Gans, 1983). Indeed, no structures morphologically or functionally resembling the vertebrate ear have been found in cephalochordates (Wever, 1974). Furthermore, *AmphiPax2/5/8*—the amphioxus homologue of the vertebrate Pax-2, -5 and 8 genes that represent some of the earliest markers for the otic placode—is not expressed in any structures that might be considered as otic primordia (Kozmik et al. 1999). In contrast, however, some urochordates (Thaliacea and adult Ascidiacea) possess mechanoreceptor cells embedded in a gelatinous cupula with striking similarity to vertebrate otic hair cells (Bone & Ryan, 1978). In ascidians, these cupular sense organs are located in the atrium which is derived from the larval atrial primordia. The primordia express the molecular marker *HrPax-258* (Wada et al. 1998) and develop next to the larval brain, invaginate—as do otic placodes—and fuse to form the atrium (Katz, 1983). Therefore, the atrial primordia have been likened to the otic placode and the atrium itself to the otic vesicle and together have been suggested to comprise the evolutionary precursors of the vertebrate ear (Wada et al. 1998; Shimeld & Holland, 2000). If these homologies hold up, this finding implies that the otic placode is a fundamental chordate feature that has subsequently been lost in amphioxus.

Within the vertebrates, the fossil record suggests that early cyclostomes had a well developed labyrinth with up to 7 semicircular canals, while extant agnathans have three or fewer canals (Wever, 1974). The common 3 canal arrangement was acquired thereafter. There are two different hypotheses about the origin of the otic placode (see also Popper & Fay, 1997). One assumes that the inner ear arose as a variation of the lateral line in fish (acousticolateralis hypothesis; Van Bergeijk, 1967; Baird, 1974*a*, *b*), while the other suggests that both the lateral line and the otic placode evolved independently from a primitive pore system containing mechanoreceptor cells (Wever, 1974). However, currently there is not sufficient support for either idea. Could developmental biology help to resolve this controversy?

In the embryo the otic placode very closely abuts the pre- and postotic lateral line placodes; in Xenopus for example these territories are so close that they merge into a continuous dorsolateral placode (Winklbauer, 1989; Schlosser & Northcutt, 2000). In zebrafish, both primordia can be identified by the homeobox gene Nkx5-1, suggesting the existence of some common molecular characteristics (Adamska et al. 2000). However, of a large number of zebrafish mutants affecting inner ear development only one—*dog-eared*—shows defects in both the lateral line and the inner ear (Whitfield et al. 1996). In addition, there are considerable temporal and spatial differences in the competence of the ectoderm to form both placodes, as well as in the timing and the distribution of the inducing signals (Stone, 1931; Yntema, 1950; Liedke, 1955; for review see: Baker & Bronner-Fraser, 2001). Furthermore, the lateral line system has been lost repeatedly during evolution without affecting the inner ear. Identifying the cellular and molecular pathways governing induction and patterning of both the otic and the lateral line placodes and their comparative analysis will help to resolve some of the questions regarding their common origin.

INDUCTION OF THE OTIC PLACODE

During development, the otic placode first becomes visible as a thickening of the ectoderm next to the hindbrain rhombomeres 5 and 6 in 8–10 somite embryos (Torres & Giraldez, 1998; Baker & Bronner-Fraser, 2001). At this time the placode has already acquired some tendency to develop autonomously: when grown in isolation it can form vesicle-like structures and continue to express some marker genes, but not others (Waddington, 1937; Yntema, 1939; Jacobson, 1963*a*, *b*, *c*; Swanson et al. 1990; Gallagher et al. 1996; Giraldez, 1998; Groves & Bronner-Fraser, 2000). In contrast, final commitment to otic fate seems to occur much later and varies considerably between experimental conditions and species (Yntema, 1933, 1939; Ginsburg, 1995; Gallagher et al. 1996; Herbrand et al. 1998); for example, in anuran amphibians the inner ear is determined earlier than in urodeles (Ginsburg, 1995). Together these observations indicate that otic induction must begin already before the placode becomes morphologically distinct and that the otic placode and/or vesicle depend on sustained signalling from the surrounding tissues for some time thereafter.

At gastrula and early neurula stages, a fairly large region of the ectoderm is competent to form an otic placode when transplanted into the future otic region (Yntema, 1933; Waddington, 1937; Jacobson, 1963*a*, *b*, *c*; Groves & Bronner-Fraser, 2000). Subsequently competence becomes restricted to a stripe of ectoderm adjacent to the hindbrain that extends considerably beyond the normal position of the otic placode (at least in chick; Groves & Bronner-Fraser, 2000). Even in a 15 somite embryo, when the otic placode is well developed, the surrounding ectoderm can regenerate an otic vesicle after removal of the original placode (Waddington, 1937). In addition, inducing signals also seem to be present in a fairly

broad region: when competent ectoderm is grafted next to the neural tube at different rostrocaudal levels, otic placodes can be induced from the level of rhombomere 2 to the level of the 2nd somite (Groves & Bronner-Fraser, 2000). Given that competence and inducing signals have such a broad distribution, how is the otic placode induced in a precise location, always adjacent to the future auditory nuclei of the brainstem?

Because of their close apposition, it has been assumed for a long time that the otic placode is induced by hindbrain-derived signals at the time of neural tube closure. Indeed, grafts of hindbrain (Stone, 1931; Kohan, 1944; Harrison RG, 1945; Kuratani & Eichele, 1993) or hindbrain precursors (Woo & Fraser, 1997) placed adjacent to non-otic ectoderm, as well as rotation of the hindbrain about the anterior posterior axis (Sechrist et al. 1994) both result in the development of ectopic otic vesicles. However, in most of these studies it remains unclear whether the otic structures differentiated from the graft or were induced in host tissue.

FGF-3 is expressed in rhombomeres 5 and 6 adjacent to the otic placode (Wilkinson et al. 1988; Tannahill et al. 1992; Mahmood et al. 1996) and was proposed to be a hindbrain-derived otic inducer, since otic vesicle formation was impaired in the presence of FGF-3 antisense oligonucleotides (Represa et al. 1991). In addition, overexpression of FGF-3 in Xenopus and chick leads to the formation of ectopic otic vesicles (Lombardo et al. 1998; Lombardo & Slack, 1998; Vendrell et al. 2000). However, mice deficient in FGF-3 reveal that while morphogenesis of the otic vesicle is affected, placode formation is initiated normally, suggesting that FGF-3 is not essential for otic induction (Mansour, 1994). Furthermore, other mutant mice with hindbrain defects—e.g. Hoxa1 (Lufkin et al. 1991; Chisaka et al. 1992) or Kreisler mutants (McKay et al. 1996), Hoxa1/Hoxb1 (Gavalas et al. 1998) and RARα/RARβ double mutants (Dupe et al. 1999)—undergo essentially normal otic induction, but show abnormalities in otic vesicle morphogenesis. It therefore seems likely that, at neural tube stages, signals from the hindbrain are required for patterning the otic vesicle rather than being involved in otic induction.

How then is otic induction initiated? Embryological experiments suggest that the induction of the otic placode is a complex process that consists of multiple events involving the interaction of competent ectoderm with different tissues (and signals) such as mesoderm, young neural plate and the neural tube (Stone, 1931; Harrison, 1935; Yntema, 1950; Jacobson, 1963*a*, *b*, *c*; Gallagher et al. 1996), which may act in combination or sequentially. While it seems clear that all these tissues play some role in otic induction, only recently has some progress been made in determining their relative contribution.

A number of studies suggested a role of mesodermal tissues in the early steps of otic induction. In amphibians, axial and nonaxial mesoderm from early neurula stages (Kohan, 1944; Raven & Kloos, 1945), lateral mesoderm (Holtfreter, 1933) and future cardiac mesoderm (Jacobson, 1963*a*) have some ability to induce otic structures apparently in the absence of neural tissue. In the chick, removal of cephalic mesoderm precursors at head-fold stages leads to a delay or absence of the otic placode (Orts-Llorca & Jimenez-Collado, 1971). Similarly, zebrafish mutants with mesodermal defects show a delay in the onset of otic marker expression (Mendonsa & Riley, 1999).

In the chick, only paraxial head mesoderm underlying the otic placode, but no other mesodermal tissue, can support otic marker expression and the development of placode morphology (Streit, unpublished observations). A recent study proposes FGF-19 as the mesodermal signal directing otic induction (Ladher et al. 2000): in the chick it is expressed in mesoderm that comes to underlie the otic placode and in the adjacent neural plate. In vitro, FGF-19 can induce some otic markers in neural plate explants, however by itself fails to do so in future otic or nonotic ectoderm. These findings suggest that FGF-19 alone is not sufficient to induce the otic placode, but that signals from the neural plate may also be involved, in agreement with the embryological experiments mentioned above. Indeed, Wnt8c (which is expressed in the hindbrain at the appropriate time; Hume & Dodd, 1993) together with FGF-19 promotes the expression of otic markers in future otic ectoderm (Ladher et al. 2000). In addition, FGF-19 can induce Wnt8c expression in the neural plate. Together these findings suggest a model in which mesoderm derived FGF-19 induces Wnt8c expression in the overlying neural plate and both factors then cooperate to initiate otic development. Future experiments will have to address the timing of these signals, whether they can act on nonplacodal ectoderm and whether they are necessary for otic induction.

In a current working model, neural tissue therefore seems to play a dual role in otic development: during early steps of otic induction it acts in concert with mesodermal signals to initiate otic development and at later stages is essential for patterning and morphogenesis of the otic vesicle.

It is noteworthy that the generation of otic placodes

by tissue grafting or re-combination or by secreted factors has only been successful in the future otic region (before it is specified) or in a region adjacent the neural plate that will give rise to other ectodermal placodes or the epidermis between them, but not in more lateral ectoderm. Interestingly, it has previously been suggested that the territory next to the neural plate represents a common placodal field from which all placodes originate and in which cells are competent to give rise to any placode (Knouff, 1935; Jacobson, 1963*c*, 1966; for reviews see Torres & Giraldez, 1998; Baker & Bronner-Fraser, 2001). The existence of such a field implies that initially all placode cells go through a 'generic placodal state' that is set up by a common molecular mechanism and that cells then diversify to acquire characteristics specific for individual placodes. Does such a primitive placodal state exist in non-vertebrate chordates? The idea is attractive and simple: it requires one molecular pathway to be recruited to specify a placode region or an ancestral placode; elaboration or modulation of the placodal state then leads to the generation of placodes with different identities. Currently, there is no conclusive evidence either against or in favour of this idea (for further discussion see: Graham & Begbie, 2000; Shimeld & Holland, 2000; Baker & Bronner-Fraser, 2001). In future, however, the careful analysis in protochordates of the expression of genes that appear to be molecular markers for the placodal territory in vertebrates may well shed some light on how the complex cranial sensory system arose during evolution.

CONCLUSION

Molecular evidence has revealed that lower chordates already possess sensory organs that share homology to the vertebrate inner ear. As the pathways that govern the development of the vertebrate otic placode are discovered, it will be interesting to investigate their conservation in lower chordates. A similar approach may also resolve the question of whether the inner ear is derived from the lateral line or whether it evolved independently.

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