

## Review

# An Integrated Perspective of Evolution and Development: From Genes to Function to Ear, Lateral Line and Electroreception

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**Abstract:** Four sensory systems (vestibular, lateral line, electroreception, auditory) are unique and project exclusively to the brainstem of vertebrates. All sensory neurons depend on a common set of genes (*Eya1*, *Sox2*, *Neurog1*, *Neurod1*) that project to a dorsal nucleus and an intermediate nucleus, which differentiate into the vestibular ear, lateral line and electroreception in vertebrates. In tetrapods, a loss of two sensory systems (lateral line, electroreception) leads to the development of a unique ear and auditory system in amniotes. *Lmx1a/b*, *Gdf7*, *Wnt1/3a*, *BMP4/7* and *Atoh1* define the lateral line, electroreception and auditory nuclei. In contrast, vestibular nuclei depend on *Neurog1/2*, *Ascl1*, *Ptf1a* and *Olig3*, among others, to develop an independent origin of the vestibular nuclei. A common origin of hair cells depends on *Eya1*, *Sox2* and *Atoh1*, which generate the mechanosensory cells. Several proteins define the polarity of hair cells in the ear and lateral line. A unique connection of stereocilia requires CDH23 and PCDH15 for connections and TMC1/2 proteins to perceive mechanosensory input. Electroreception has no polarity, and a different system is used to drive electroreceptors. All hair cells function by excitation via ribbons to activate neurons that innervate the distinct target areas. An integrated perspective is presented to understand the gain and loss of different sensory systems.

**Keywords:** neurons; brainstem nuclei; hair cells; bHLH genes; *Sox2*; *Eya1*; *Lmx1a/b*



**Citation:** Fritsch, B. An Integrated Perspective of Evolution and Development: From Genes to Function to Ear, Lateral Line and Electroreception. *Diversity* **2021**, *13*, 364. <https://doi.org/10.3390/d13080364>

Academic Editors: Raul E. Diaz and Michael Wink

Received: 17 June 2021

Accepted: 27 July 2021

Published: 7 August 2021

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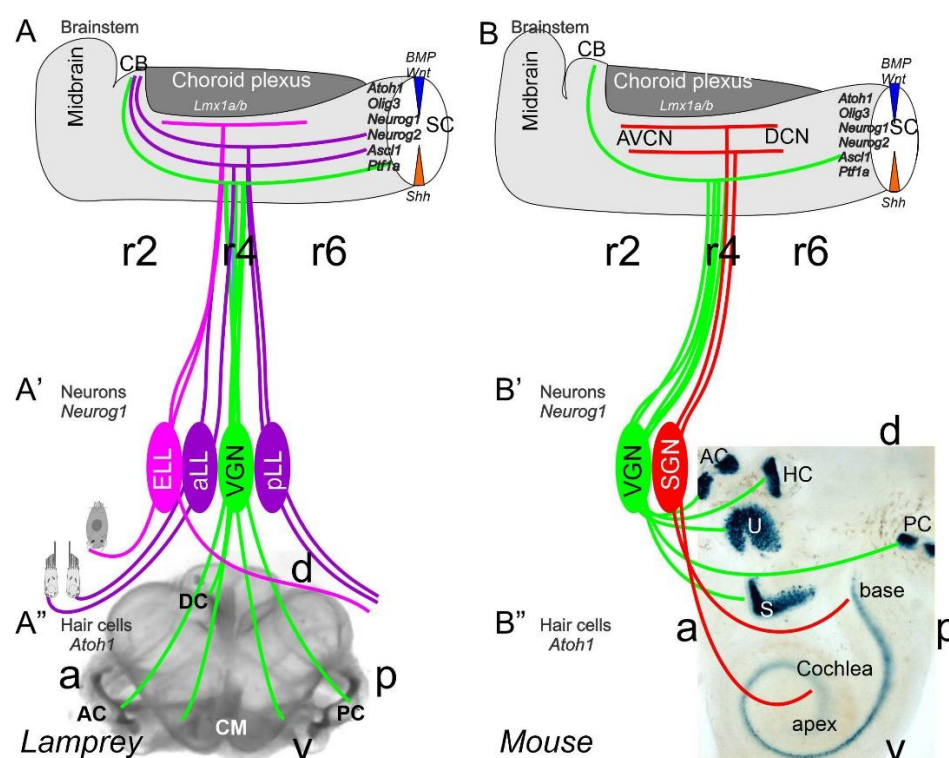
## 1. Introduction

Sensory maps depend on the specific sensory modality and the relevant information to be extracted by them. Beyond primary sensory maps, central map formation underlies the integration of various sensory modalities, namely the ear, lateral line and electroreception. The four primary sensory maps of vertebrates have unique features and seemingly use distinct molecular cues, cell cycle exit and activity combinations during development, regeneration and plasticity. The evolution of chordates is comparable with the organization of the dorsal spinal cord and brainstem, which is associated with neurons and hair cells in 71,000 vertebrates. On the other hand, we have limited support for the two chordates associated with the neural crest and placodes, hair cells and central brainstem in 31 species of lancelets and 3100 species of ascidians. Fossils appeared approximately 540 million years ago (Mya), and all major bilaterian phyla presented by 500 Mya [1].

The brainstem of vertebrates is organized into rhombomeres (r0-11) that superficially resemble other chordates, lancelet and ascidians [2–4]. A dorsal part of the brainstem expresses a continuation to the spinal cord in vertebrates [5] which is absent in a true brainstem in other chordates. Partial similarity is found in ‘dorsal root ganglia’ in ascidians that resembles the spinal cord in vertebrates, which is absent in lancelets [2,6,7]. Adding these differences in chordates, gene duplication [8], followed by diversification [9,10], is the basis for the unique brainstem, neurons and hair cells that developed in vertebrates [11]. The unique formation of mechano- and electroreception evolved in four distinct sensory inputs that are partially similar with the lateral line of ascidians [6,12–14]. The progression must start with the sensory neurons that connect all neurons with the brainstem and reach out the peripheral sensory hair cells.

Neurons depend upon *Eya1* [15], *Sox2* [16], *Neurog1* [17] and *Neurod1* [18]. In contrast to *Neurog1* null mice, which showed a complete loss of neurons [19], *Neurod1* null mice showed residual neurons extending centrally to smaller vestibular and cochlear nuclei [20,21] that reached the ear [22,23]. It is worth noting that the lateral line and electroreception are separate for the vertebrate ear that is lost in most tetrapods to generate novel cochlear neurons, the spiral ganglion neurons (Figure 1).

The brainstem is a continuation of the spinal cord (SC; [11,24,25]) that develops into rhombomeres and differentiates into nuclei, namely the vestibular, lateral line and electroreception nuclei in basal vertebrates (Figure 1). Loss of the lateral line and electroreception leads to the development of cochlear nuclei in tetrapods [26,27]. All dorsal expression of the brainstem depends on *Lmx1a/b* [28] and *Gdf7* [29], which drive the choroid plexus (Figure 1). Combined, *Lmx1a/b* and *Gdf7* regulate the formation of *Wnt1/3a*, *BMP4/7* and *Atoh1*. This formation is likely reduced or absent in *Neurog1/2*, *Ascl1*, *Ptf1a* and *Olig3*, among others (Figure 1).



**Figure 1.** Inner ear, lateral line and electroreception revealed. Neurons (*Neurog1*; A') form vestibular ganglia (VGN) to reach out 4 hair cell organs in lampreys (A''). A separate lateral line (LL) and electroreceptor neurons (ELL) that innervate hair cells project more dorsal in lampreys. Central projection depends on *Atoh1* to receive LL and ELL fibers, whereas several bHLH genes (*Neurog1/2*, *Olig3*, *Ascl1*, *Ptf1a*) receive all VGN (A). In the absence of ELL and LL development in amniotes, mammals develop separate spiral ganglion neurons (SGN; B') that extend from the cochlea (B'') and end in a topological central projection that depends on *Atoh1* (B). The formation of VGNs (*Neurog1*; B') reach the 5 hair cells (B'') to extend the distribution of bHLH genes. Note that certain areas are lost or gained which enter central projections near r4. Images are shown by *miR-183* ISH (A'') and *Atoh1*-LacZ (B''). AC, anterior crista; AVCN, anteroventral cochlear neurons; CB, cerebellum; aLL, pLL, anterior/posterior lateral line neurons; CM, common macula; DC, dorsal crista; DCN, dorsal cochlear neurons; HC, horizontal crista; PC, posterior crista; r2/4/6, rhombomeres; S, saccule; SC, spinal cord; U, utricle. Modified after [11,30,31].

Mechanosensory and electrosensory hair cells (Figure 1) depend on *Eya1*, *Sox2* and *Atoh1* to initiate the cell cycle and to differentiate into vestibular, cochlear, lateral line and

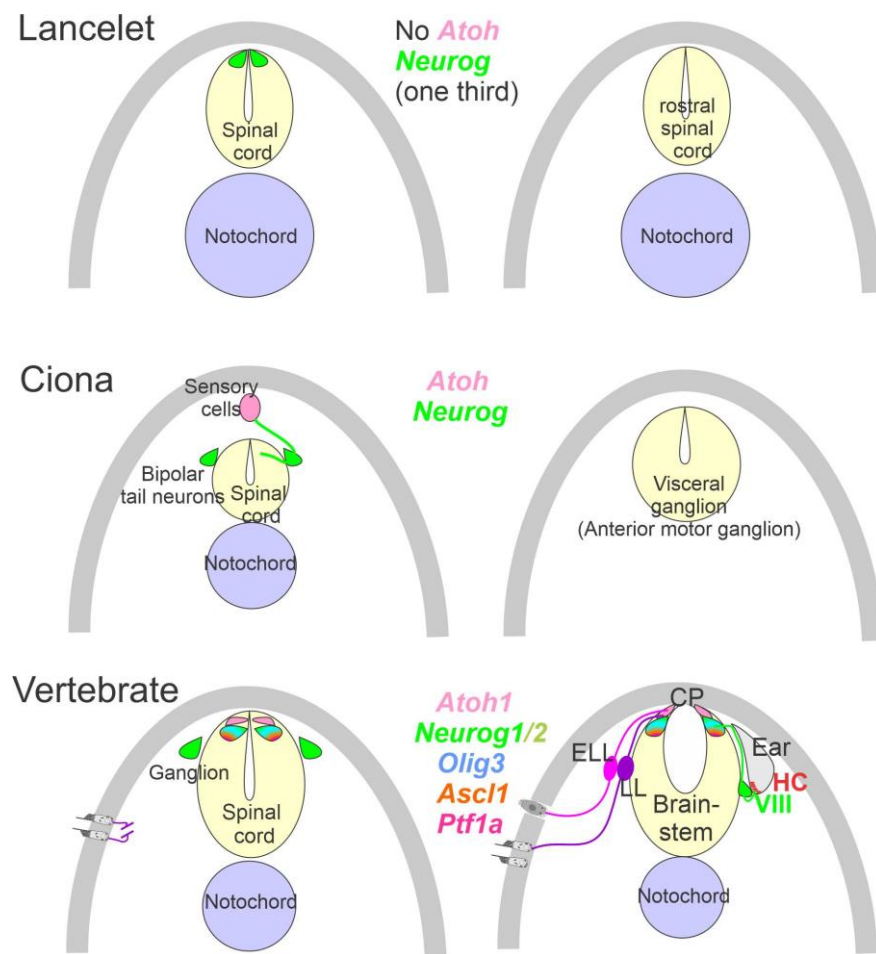
electrosensory hair cells [22,32,33]. Planar cell polarity (PCP) depends on the formation of shifting the central projection of the kinocilium into a lateral position. PCP extends the length of the stereocilia to develop the staircase of tip links of the vestibular, cochlear and lateral line hair cells [34–36]. The next step involves the development of the tip links to allow the connections between *CDH23* and *PCDH15* to open up the channel to form a mechanosensory hair cell [37,38], with opposing polarity in most of the ear and lateral line [34,39–41]. *TMCI/2* provides a major function that seems to interact with additional channel proteins (*TMHS*, *TMIE*), forming a complex interaction [37,42–44]. In contrast, while the electroreception forms next to lateral line hair cells [22,23,45], these hair cells lack any polarity organization, and certain ampullary hair cells are dependent on *Ca<sub>v</sub>1.3* [46].

This review will compare the three neurosensory components that form the neurons which, on the one hand, connect to the brainstem for input, and, on the other hand, receive the hair cells for sensory input. Gene regulation of neurons, central nuclei and hair cells is driven by gene duplication and diversifies after chordates diverge from vertebrates [10], leading to the gain and loss of three sensory systems (lateral line, electroreception, auditory). Gene regulation explains the diversification of the vestibular system from three hair cells up to nine hair cell populations, including the cochlea of mammals [3,47].

## 2. Neurons Depend upon *Eya1*, *Sox2*, *Neurog1* and *Neurod1*

The ear, lateral line and electroreception neurons depend on genes that, collectively, define their development. Upstream of bHLH genes, which initiate the proliferation of neurons, is the expression of *Eya1*, which interacts with *Brg1* to initiate pro-neurosensory development [15,48,49]. In the absence of *Eya1*, there is no neuronal development that allows ear formation, and neither neurons nor hair cells differentiate [15]. Evolving neurons start in the lancelet, which lack dorsal root ganglia. The dorsal root ganglia show partial expression of *Neurog* inside the spinal cord (Figure 2), which lacks an *Atoh* gene [50,51]. In contrast, at least a smaller set of bHLH genes are partially characterized in the developing ascidian, *Ciona* [52], which have at least six bHLH genes driving neuron development: *Ptf1a*, *Tcf3*, *Atoh*, *Ascl* and *Neurog* [7,12]. A detailed serial section analysis shows the innervation of sensory cells (*Atoh*) from fibers of the neurons (bipolar tail neurons; Figure 2) that can trace to reach the anterior motor ganglion [13]. Neither the full expression of *Eya* nor *Sox2* outside the neural plate are unclear in the lancelet and tunicates [2,52].

A crucial next step is the initiation of *Sox2*, which is needed to upregulate *Neurog1* [53–55]. In fact, *Sox2* delays certain neuron development in bony fish [56], and in the presence of *Sox2* is unclear the sequence of gene regulation in the lamprey and hag-fish [57]. There is a distinct effect of the loss of early genes in the vestibular ganglion, which initially differentiates in the absence of *Sox2* and *Neurog1* (Figures 1 and 2) and does not develop in the auditory neurons [16]. A loss of all auditory neurons, and partial loss of vestibular neurons, are known for *Pax2* [58], *Gata3* [59], *Lmx1a/b* [28], *Fgfr2* [60], *Shh* [61] and *Dicer* [62]. Partial loss of some vestibular neurons are known for *Fgf10* [63] and *Foxg1* [64,65], indicating a limited loss of sensory hair cells and/or neurons. Unfortunately, the details of the lateral line and electroreception (Figures 1–3) are not as fully genetically characterized [22,23,27,33]. The lateral line and electroreception likely depend on neuronal development (Figures 1 and 2), including the development of spinal ganglia neurons [66] and trigeminal neurons [67–69]. A separate placode is derived from neurons that develop from *Neurog2* in mammals [68,70]. In birds, this placode is driven by *Neurog1* [71,72]. Furthermore, separate amniotic paratympanic placodal neurons innervate separate hair cells that partially integrate into the central vestibular projection [72].



**Figure 2.** Neurons require *Neurog* expression. Lancelets have a limited description of bHLH genes that are characterized in the more caudal spinal cord, which is positive for *Neurog*. Note that the lancelet has no *Atoh* bHLH gene. *Ciona* has at least 6 bHLH genes expressed in sensory cells that are innervated by bipolar tail neurons which extend to reach the visceral ganglion for interactions. *Atoh* and *Neurog* genes are described in *Ciona* associated with the spinal cord. Vertebrates have dorsal root ganglia that depend on *Neurog1/2*, which is also expressed in *Atoh1* and *Neurog1* of the spinal cord. The brainstem is innervated by electroreceptor (ELL) and lateral line fibers (LL) that extend to innervate migration populations of LL and some ELL). The ear is unique in vertebrates, which give rise to the VIII ganglia that innervate more ventral nuclei compared to LL and ELL projections to reach *Atoh1*. CP, choroid plexus. Modified after [2,7,12,23,24].

In addition to directly initiating the formation of neurons by *Eya1*, *Sox2*, *Pax2* and *Neurog1/2*, another set of genes are regulated to differentiate into *Neurod1* [18,20,21,71,73], followed by *Isl1*, *Foxg1*, *Pou4f1* and *Phox2b* [71,74–76], which interact with *Shh*, *BMPs* and *Wnts* to define neurons [77,78]. Regional regulation of the distinct vestibular, lateral line, electroreception and auditory neurons are sorted out by downstream genes regulating the distinct innervation. For example, the expression of *Calbindin*, *Calretinin*, *Pou4f1* and *Peripherin* is required to sort out the innervation from the inner and outer hair cells [79–82]. In *Sox10* null mice, an interaction showed disorganized cochlear neurons, whereas the development of vestibular neurons was near normal [83]. This interaction is consistent with the loss of *Erb2* of nearly all cochlear neurons, as well as reduced vestibular neurons [84]. The concept of having multiple sources of neurons from the placode and neural crest is likely due to a misinterpretation [3,83,85–87].

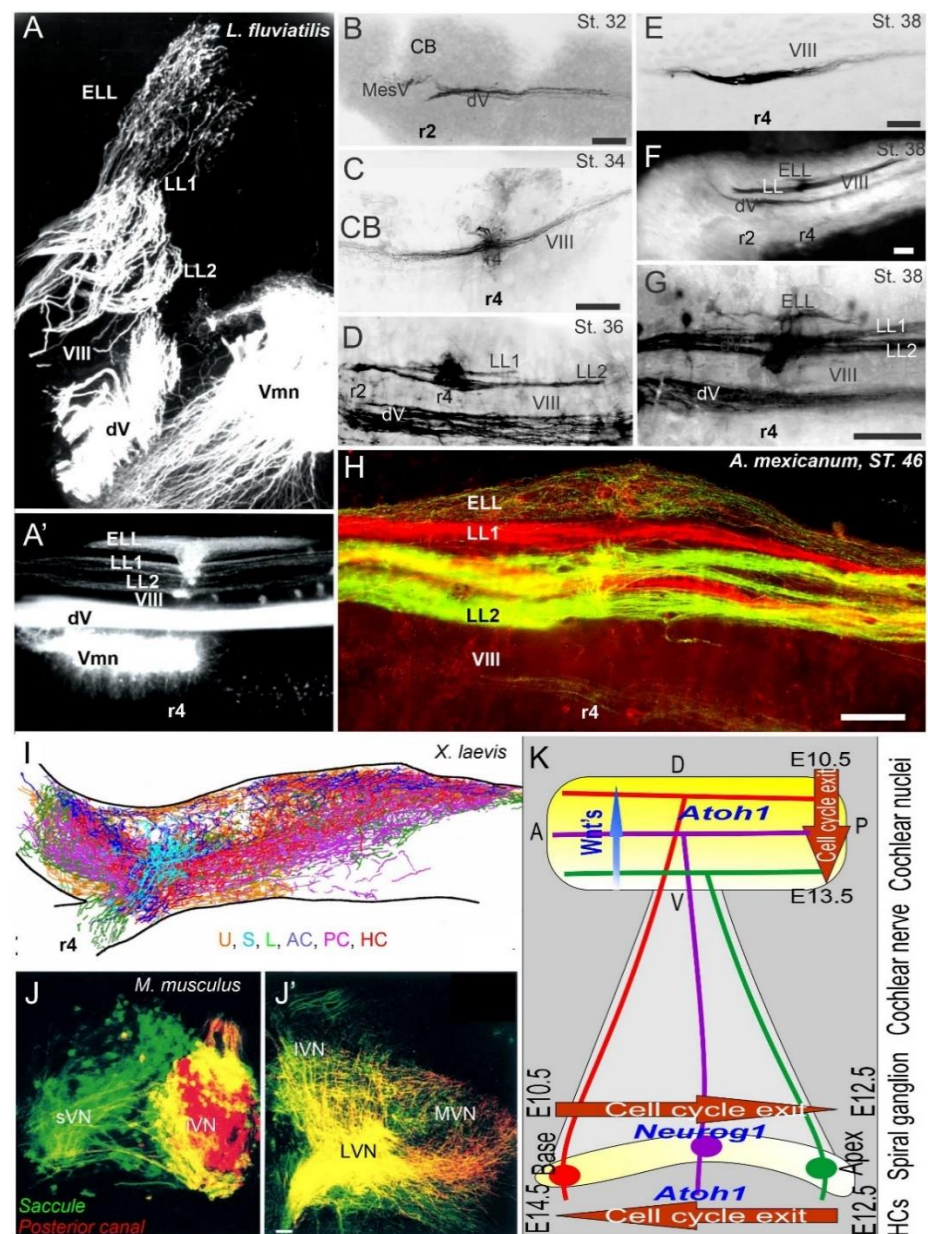
Downstream of gene development, the expression of *TrkB* (*Ntrk2*) and *TrkC* (*Ntrk3*) has a reduction and loss in vestibular and cochlear neurons. Vestibular neurons are

mostly dependent on *TrkB* [88,89] whereas the cochlear neurons are mostly dependent on *TrkC* [90,91]. Loss of both neurotrophin receptors causes the early loss of all neurons [92–94]. Limited expression is characterized in some ascidians which are unknown in the lancelet [1]. The comparable expression of the lateral line and electroreception are unclear due to the multiplication of neurotrophins in bony fish [95,96].

The proliferation of neurons and hair cells depend on *MycN* [97,98], which drives the division of the G1, S and G2 phases with a set of genes that interactions with cell cycle regulation [53,99–101]. Detailed characterization and proliferation have been described in the ear and brainstem, clarifying cell cycle progression in mice and rats [102–104]. *Sox2* and *Neurog1* are in negative feedback, which allows proliferation and initiates differentiation. This differentiation interacts with retinoblastoma (*Rb*), *Hes/Hey* and *ID*s to regulate the cyclin-dependent kinases (CDKs), cross-react with e-proteins and define whether a cell cycle is progressing [98,100,105,106]. In the end, continuation depends on either knocking out *Rb* to continue proliferation or upregulating of *Sox2* to jumpstart proliferation [107,108].

In various vertebra, the central projection has been described to show the projection of the vestibular, lateral line, electroreception, and cochlea [3,67,87,109–111]. Three sets of central projections are known in vertebrates that develop a loss of the lateral line, electroreception and added cochlear nuclei [23,26,112]. For electroreception, these central projections always have a single set of an anterior ganglia (Figures 1 and 3) that adds variably the electroreception in bony fish [27,113]. Lateral line neurons (Figures 1–3) can be split into an anterior and posterior branch that diversify the neuromasts to innervate all lateral line hair cells (Figure 3; [114–116]). Vestibular neurons have two neuron populations in hagfish [57], while lampreys and jawed vertebrates have a single vestibular ganglion [111,117,118]. At least 4–5 distinct innervations are described in lampreys [119,120], whereas most gnathostomes have at least five and up to nine branches of vestibular and auditory connections (Figures 1 and 3): three canal cristae, utricle, saccule, lagena, basilar papilla, amphibian papilla and neglecta [121,122]. Branches of discrete neurons are known for an anterior and a posterior (superior) nucleus that innervates two canal cristae (anterior and horizontal cristae), the utricle and part of the saccule (Figure 3). The remaining part of the utricle provides a posterior canal and the branch of the saccule (Figures 1 and 3) in mammals [123]. The development of central projections follows a simple layout. First, the trigeminal and epibranchial neurons develop. Then, central projection follows. Subsequently, vestibular, lateral line and electroreception develop, if present (Figure 3; [3,124]). Different developmental patterns exist in neuronal proliferation: nearly all neurons continue proliferation for a long time or lifetime, whereas mammals have an early production of neurons that ends proliferation very early [67,125,126]. The topology of peripheral neurons of the vestibular, lateral line and electroreceptors is unclear, suggesting an overlap with an incomplete segregation of neurons that is well known for the vestibular neurons (Figure 3 [123]).

A long-term proliferation of the vestibular, lateral line and electroreception is followed by a delayed formation of cochlear neurons, the spiral ganglia neurons (SGN), which follow vestibular neurons in mammals (vestibular neurons: E9–11; SGN: E10–12 [125,127]). A unique topological development is known among mammals [128], first showing the basal turn neurons (Figure 3), which reach the anteroventral, posteroventral, and dorsal cochlear nuclei (AVCN, PVCN, DCN). The development of these neurons is followed, with delay, by the apical neurons [67,87,110,129]. Interestingly, there are central projections that can form independently to reach the formation of cochlear nuclei [130]. In the absence of target hair cell development [92,131], cochlear neurons develop and largely proliferate prior to cochlear nuclei and cochlear hair cells (Figure 3). Central cochlea require the expression of *Neurod1*, *Wnts*, *Fzd*, *Npr2* and *Ephrins* for targeted central projections [21,129,132,133].



**Figure 3.** Central projections form afferents to distinct innervation. The lateral line of 2 or more branches form, whereas electroreception receives the short dorsal projection in lampreys (A,A') and salamanders (B–H). Vestibular projection forms after the trigeminal central projection, followed by the lateral line and electroreception (B–H). Central projection in a frog (I) and mammal (J,J') show the incomplete distribution of distinct neurons (J) that overlap and incompletely segregate the vestibular projection (I,J'). Spiral ganglia (K) proliferate neurons in a base to apex progression (E10.5–12.5) that reach the central projection to form a topology from dorsal to ventral cochlear nuclei (E10.5–13.5), depending on Wnt expression. Later, hair cells proliferate from apex to base (E12.5–14.5) that reach the afferents. AC, anterior crista; dV, trigeminal afferents; ELL, electroreception; HC, horizontal crista; LL1/2; lateral line; L, lagena; LVN, lateral vestibular nuclei; IVN, inferior vestibular nuclei; iVN, inferior vestibular neurons; MVN, medial vestibular nuclei; PC, posterior crista; S, saccule; sVN, superior vestibular neurons; U, utricle; Vmn, trigeminal motoneurons; VIII, vestibular projections. Modified after [3,23,67,123].

In contrast to the topology of the cochlear nuclei [11,128], the central vestibular neurons have an incomplete central segregation (Figure 3) that shows both segregation and overlap from different vestibular neurons [3,123,134]. Lateral line central projections can

be segregated in certain vertebrates but show an overlap in other vertebrates [3,23]. For electroreception, multiple central topological projections in certain bony fish [27,135] show an overlap in lampreys and salamanders (Figure 3 [23,109]). The vestibular, lateral line, electroreception and cochlea independently reach hair cells that form prior to neurons [23,136], consistent with the same pattern of neurons that develop first, followed by the central axon to the brainstem, and later followed by the hair cell innervation [3,109,134,137]. This is obvious in cases where hair cells are not formed, such as in *Atoh1* null mice, which show a near-normal central projection [131,138]. A similar central projection forms after the loss of hair cells in *Pou4f1* null mice [139]. Loss of formation of a specific set of hair cells is demonstrated in the posterior canal that projects normally, despite the absence of *Fgf10* [63], which degenerates later.

In summary, the neurons of the ear, lateral line and electroreception are generated by a set of genes that act downstream of *Neurog1* to initiate the cell cycle. Neurons develop independently of central axons and reach innervate the hair cells shortly after proliferation. Segregation of central projections can be topologically organized in the auditory central projection of most tetrapods, and present two lateral line neurons that segregated in many vertebrates. Some central topology found in some, but not all, lateral line and electroreceptors, show an incomplete segregation for the vestibular neurons.

### 3. The Brainstem Is Transformed from the Spinal Cord

The spinal cord and rhombomeres (r0-11) of the brainstem [140,141] are basically identical in terms of the distribution of overall gene expression [24,25]. The distribution of gene expression in the spinal cord and rhombomeres differentiates into a unique population of r0-7 [142–145]. The earliest genes—*Gemini* (*Gmn*), *Zic* and *Foxd4* [146–148]—define the neural ectoderm, which cooperates with *Smarca/Brg*-related genes to induce neural ectoderm. Certain interactions can become more complicated and can, for example, be downstream from *Zic1* by *Wnt1* and cooperate with *Fgf*, *Noggin/Chordin* and *Nodal*, which counteract with *BMPs* while *Dkk/Cerberus* counteracts *Wnt*. Interestingly enough, certain aspects of *Wnt* are independently regulated from *Wnt3a*, defining more variations among the large family of *Wnts* [149,150]. A major role for the invaginating of neuroectoderm depends on *Shh* and *Gli* to induce ventral formation, which counteracts with *BMPs* and *Wnts* to define the dorsal part of the brainstem and induces the motoneurons [4,151,152].

Recent work has shown that a unique formation of the choroid plexus in the brainstem depends, at least, on two genes: *Lmx1a/b* and *Gfp7* [29,153,154]. In the absence of *Lmx1a/b* double-null mice, the choroid plexus disappears (Figure 4), transforming the dorsal part of the brainstem and cerebellum into a continuation from spinal cord to the midbrain [11,28].

Gene expression of *Eya1* [74,155], followed by *Sox2* [15,53,54], is needed to upregulate proneuronal formation. In addition, a set of bHLH genes [5,24,25] is required to initiate the formation of neurons. Only two bHLH genes, *Atoh1* and *Olig3*, are expressed throughout the spinal cord and brainstem [5,25,156] that is diversified in the more rostral part of the brainstem into the cerebellum and auditory nuclei [157]. The formation of all neurons that depend on *Atoh1/Olig3* shows complete loss of all *Atoh1* expression genes [158]. This formation has been demonstrated using *Wnt1-cre* upstream of *Atoh1*, leaving only the choroid plexus in *Atoh1* null genes [130,156]. In contrast, some *Atoh1*-positive cells develop in *Olig3* null mice that have changed the definition of the effect without *Olig3* [145,159]. Loss of *Gdf7* [29] and *Lmx1a/b* double-null mice [154] abolishes *Atoh1* expression, *Olig3* remains that may or may not expressed in *Gdf7/Lmx1a/b* mice (Figure 4).

A complex interaction is generated by feedback loops. J Johnson showed the cross-repression of *Atoh1-Neurog1* in a reciprocal interaction to sharpen the boundaries of *Atoh1* and *Neurog1/2* in the spinal cord [24]. Different expression levels define (from roof plate) *Atoh1*, *Neurog1/2*, *Ascl1* and *Ptf1a*. In addition, roof plate is regulated by *Gdf7* and *Lmx1a/b* to follow a gradient of high levels of *BMP* and *Wnt*. *Atoh1-Neurog1/2* is not only repressed, but is also expanded by *Ascl1*. This expansion defines most ventral fate and expresses

*Neurog1/2* adjacent to the same expression. *Ptf1a* is, again, a repression interaction with *Ascl1* and defines a subdomain in the spinal cord [24] and brainstem.

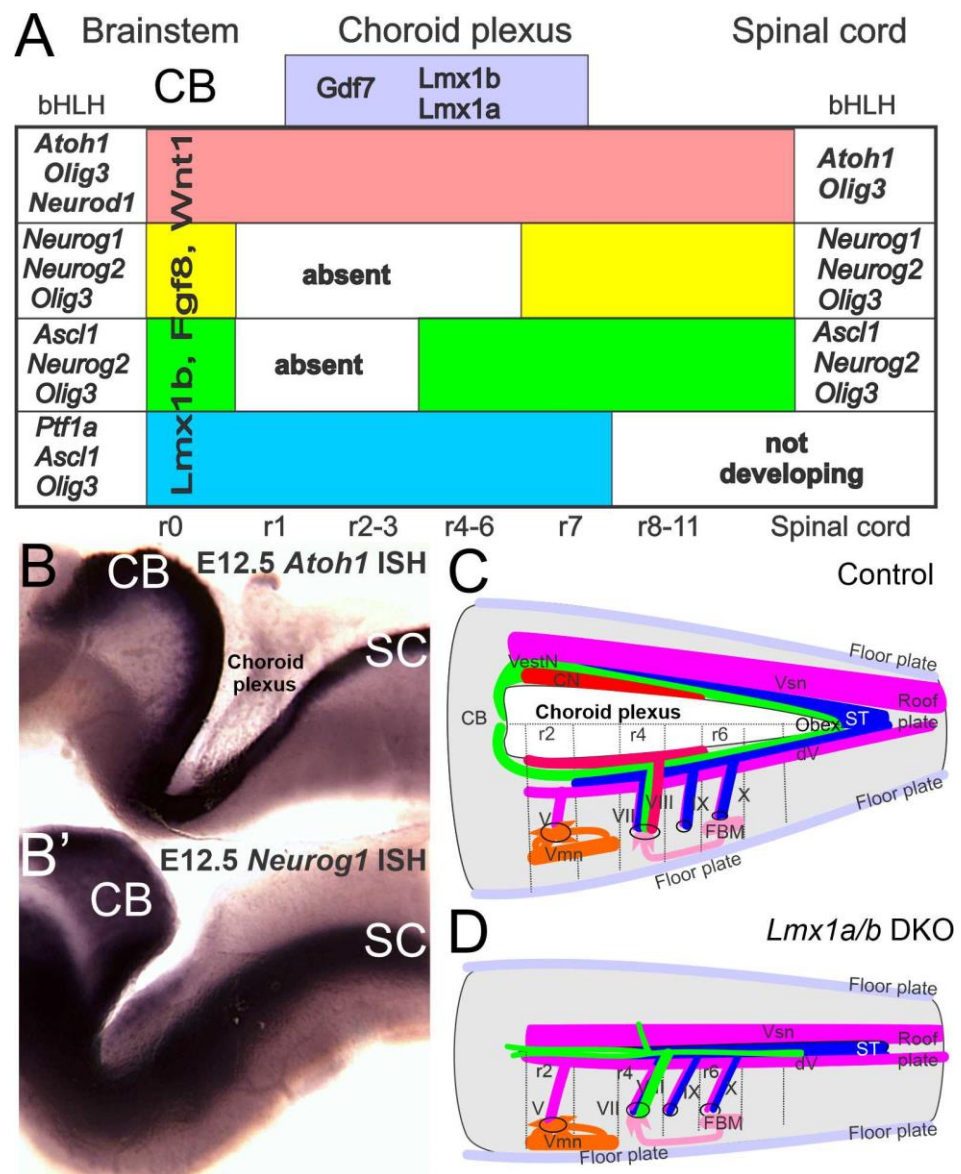
In comparison to the spinal cord, certain gains and losses of domains are clear. For example, another unique step is driven by an apparent *Ptf1a* duplication in the brainstem [25], which results in *Ptf1a* null mice, a specification of more dorsal into a different state of r0-7 [142,143,145]. More complex loss of *Neurog1/2* in r1-6 and part of *Ascl1* in r1-3 replaces the more dorsal expression of *Ptf1a* [25,143]. A more rostral reduction of these two domains requires additional research to explain the distinct effects of *Ptf1a* null mice [142,143]. In essence, the spinal cord has six identical domains (A1-3, B1-3) that differ from the rhombencephalon, showing the differential gains and losses of two domains (dA2, dA3). The spinal cord has the ability to develop two additional domains, for a total of eight domains, (A1-4, B1-4) which highlights the gains and loss of selective bHLH genes [25].

In addition to this cross-interaction, the spinal cord is further expanded by another bHLH set of genes, the *Hes/Her* genes [53,160] and the *ID* genes [9,99,161]. Starting with *Sox2* expression, the neurosensory precursor cells are self-renewing and are driven by the *Hes*, *ID* and *Myc* genes to enhance proliferation [105]. The expansion changes by an oscillation to interact with *Hes/Ascl1*, for example. It is important to understand that the *Notch* interaction allows neurons to differentiate while precursors remain as neural stem cells. In the dorsal part of the spinal cord and brainstem, the genes interact with *Atoh1*, *Neurog1/2*, *Olig3*, *Ascl1* and *Ptf1a* among proneuronal bHLH genes. Diversity is driven by distinct ways to generate astrocytes. In contrast to a downregulation of *Hes/Id/Myc*, *Sox2* is essential for neurosensory cell formation to differentiate in astrocytes that remain in *Hes*, *Id* and *Sox9*, among others [54]. In contrast, oligodendrocytes are equally downregulated, such as in neuronal differentiating cells through upregulation by *Olig1/2* and *Sox10*.

*Atoh1*, *Neurog1/2*, *Olig3*, *Neurod1* and *Ptf1a*, among others [145,157], define the cerebellum (Figure 4). A delayed expression of *Neurod1* adds to the interaction by providing negative feedback for the cerebellum of at least *Atoh1* [157,162], which expands along the auditory nuclei for feedback. Likewise, identical expression in the hindbrain shows a near-equal expression of *Atoh1* (rostral) and *Neurod1* (caudal). However, in the adult system, a different level of *Atoh1*, which shows a much higher level of expression in the auditory nuclei, supposedly counteracts with *Neurod1* out of two nuclei, particularly the dorsal cochlear nucleus [157]. In summary, the cerebellum depends on multiple genes (*Olig3*, *Atoh1*, *Neurod1*, *Ptf1a*, among others), and the exact genes are unclear in lamprey and hagfish [145,157,163].

*Lmx1a/b*, *Fgf8* and *Wnt1* delineate the cerebellum [141,152,153]. In the absence of *Lmx1a/b*, fibers branch to reach unusual central projections of vestibular fibers that receive fibers from the trigeminal and the solitary tract, crossing the nearly closed roof plate (Figure 4). Consistent projections receive the innervation from the vestibular neurons or can expand to reach lateral line fibers in vertebrates (Figures 1 and 4). Neither the electroreception nor the cochlear fibers expand to reach the cerebellum that do not expand beyond r2 (Figures 1 and 4). Certain changes in the auditory fibers can transiently trace to reach the cerebellum in certain mutations [129,164] that never directly reach the electroreceptors [27,135].

Higher projection to the midbrain and telencephalon is known among auditory, vestibular, lateral line and electroreceptions. However, this topic is out of the scope of this review [3,26,27].



**Figure 4.** The brainstem depends on *Lmx1a/b*, *Gdf7* and bHLH genes. The choroid plexus is unique, forming in the brainstem. The choroid plexus depends on *Lmx1a/b* and *Gdf7* (A), and is replaced for the roof plate in the spinal cord (C,D). Downstream are bHLH genes that have been identified in the *Atoh1* (A,B), *Neurog1* (A,B'), *Neurog2*, *Neurod1*, *Ascl1*, *Olig3* and *Ptf1a*. Certain expression is unique for the vestibular and auditory nuclei: *Ptf1a* is a duplication of ventral genes that are replaced by more rostral genes (*Neurog1*, *Ascl1*). *Lmx1b*, *Fgf8* and *Wnt1* are common cerebellums (CB) of r0. In the absence of *Lmx1a/b* and choroid plexus, no cochlear nuclei form and vestibular, trigeminal and solitary tract interact across the roof plate (C,D). dV, trigeminal fibers; FBM, facial branchial motoneurons; ST, solitary tract; V, VII, VIII, IX, X, afferent fibers; Vmn, trigeminal motoneurons; Vsm, trigeminal nucleus. Modified after [28,82,157].

In summary, the four dorsal nuclei depend on bHLH genes that define a complex interaction by the gain and loss of other bHLH genes that cross-correlate, for example, *Atoh1* and *Neurod1* in the cerebellum and auditory nuclei. Without *Lmx1a/b*, there is a loss of the choroid plexus, as well as the loss of *Atoh1* and likely other more dorsal brainstem genes (*Neurog1*, *Neurog2*, *Neurod1*, *Olig3*, *Ascl1* and *Ptf1a*).

#### 4. Hair Cells Depend on *Eya1*, *Sox2* and *Atoh1*

Mechanosensory hair cells are shared among the vestibular, cochlear, lateral line, electroreceptor and Merkel cells, a unique late addition to trigeminal sensory information [3,11,135,165]. Hair cells and Merkel cells depend on *Atoh1* for differentiation [166,167]. Evidence suggests that hair cells evolved from single-cell organisms, called choanoflagellates [32,47], which transformed a single kinocilium surrounded by villi (Figure 5) into distinct hair cells, the mechano- and electrosensory hair cells. In addition to vestibular hair cells, the inner ear forms a set of 3–9 patches of hair cells, including the cochlear hair cells (Figure 1; [117,122]). Lateral line hair cells distribute from small clusters of hair cells, referred to as neuromasts (Figure 5), to form a large set of hair cells in sharks [23,115]. Electroreception can subdivide into the ampullary organs of basic vertebrates, various additional bony fish have evolved several sets of ‘electroreceptors’ (Figure 5; [22,27,46]).

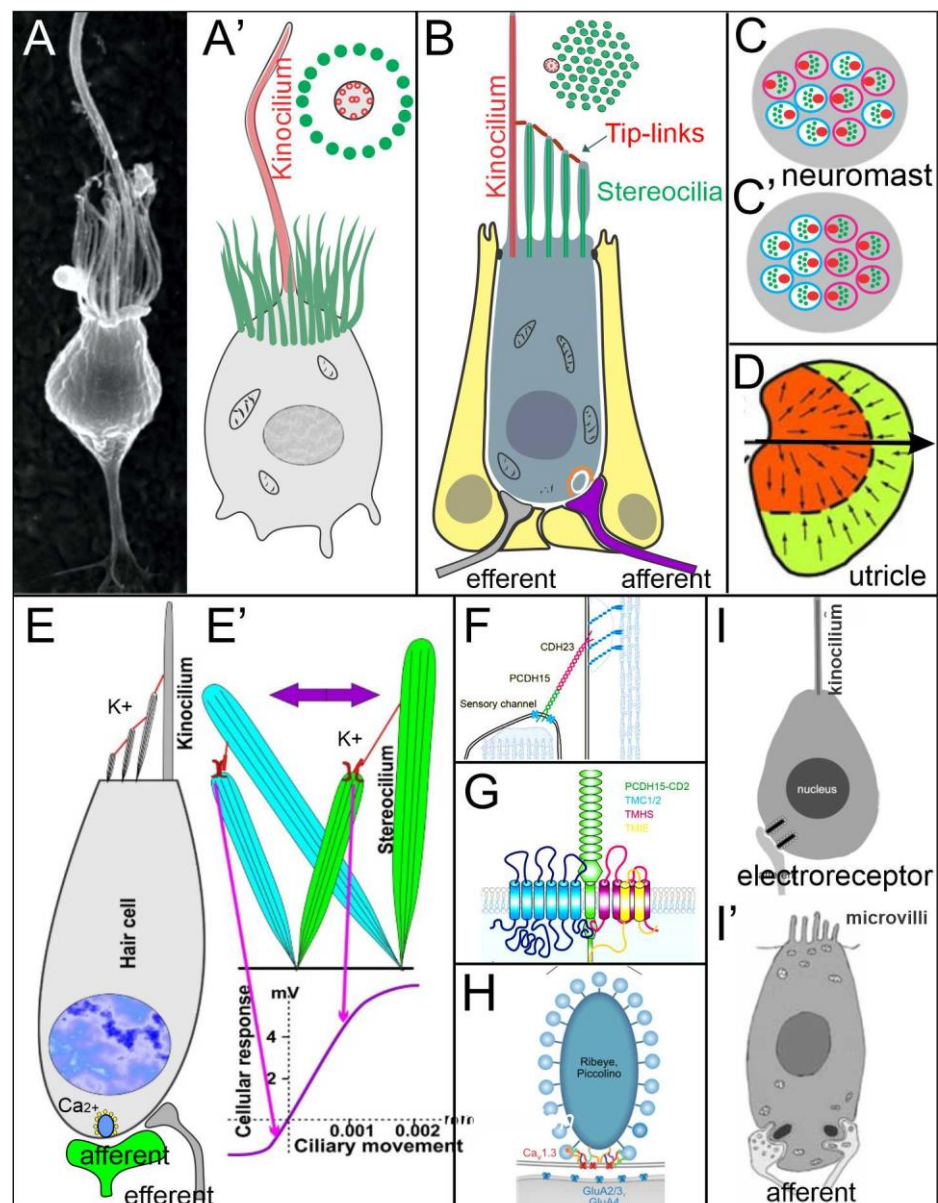
The vestibular ear requires a set of transcription genes to initiate the placode formation, starting with *Foxi3* [168] and *Fgf3/10* [63,169,170]. Downstream are *Eya1/Six1* [49,171], *Pax2/8* [58,172], *Shh* [78,173], *BMPs* [174,175] and *Wnt's* [176–178] to form the otocyst, among other necessary genes [179], where they interact to define the dorso/ventral, anterior/posterior and lateral/medial divisions to develop the otocyst [180,181]. Further downstream is the expression for *Sox2* upregulation [16,182]. *Sox2* upregulation sets up the differentiation into hair cells, which depends on the cross-interaction of *Atoh1* with *Neurod1* [21,183], *Pou4f3* [139,184,185], *Gfi1* [184,186], *Srrm/Rest* [187,188] and *Barhl1* [189,190], among others, which differ in efferent and afferent innervation [191–194].

Vestibular hair cells form maculae for gravistatic reception and canal cristae for angular receptions [47,195,196]. Polarity depends on function, but the distribution of hair cells differs. Only maculae have opposing maculae (Figure 5), whereas canal cristae are uniform in their polarity [117,191,196]. Canal cristae are also present in most auditory hair cells [122,197]. Sensory hair cells form Type I and Type II hair cells in amniotes have a common organization. All vertebrate hair cells have stereocilia organized in a staircase pattern, displaying distinct apical polarities for stimuli to open mechanoelectrical transduction channels (METs) by tip links using PCDH15 and CDH23 (Figure 5), permitting endolymphatic potassium to enter the HCs and change their resting potential [37,197,198]. The mammalian mechanosensory channel is, in part, formed by the transmembrane proteins *Tmc1* and *Tmc2* [38,199]. Other interactions are known, but these interactions require additional work for the MET formation (Figure 5). A unique formation of vertebrate hair cells is found in the *Tmc1/2* single gene in cyclostomes [43]. *Tmc1/2* is separated from the closely related gene, *Tmc3*. However, the function of *Tmc3* is unclear nearly all animals, including basic animals, for which there is no information regarding its function.

Planar cell polarity (PCP) genes depend on *Frizzled*, *Prickle*, *Disheveled*, *Van Gogh*, *Diego* and *Flamingo* for normal development [200,201]. Polarization depends on *Emx2* [41], which eliminates the contralateral organization in the utricle by converting it into a single polarity [202,203]. In addition, retinoic acid (RA) sets up various gradients [204]. Saccul and lagena have a different polarity. Instead of polarizing each other again in the utricle, they flip to organize in the saccul and lagena [191]. A distinct pattern of the utricle and saccul have a separate innervation from the cerebellum to reach one polarity (Figure 5D) and receive a descending branch of the caudal vestibular neurons [21,134,205] to end up in a different innervation (Figure 5D).

The functional unit of the lateral line system is the neuromast, which physically couples hair cells to the surrounding medium [206]. Within a neuromast, the hair cells are organized in two opposing polarities that are either randomly distributed within a neuromast or occur in a regularized counter-organization (Figure 5). The transduction from the mechanical stimulus requires an eccentric kinocilium and shorter stereocilia [207]. The absence of *Tmc1*, *Tmc2* or TMIE disrupt stereocilia development [208]. It seems possible that the neurons giving rise to the two afferents, and possibly also the two opposing hair cell populations, are separated by different birthdates in teleosts [124,209]. In zebrafish, it was

further shown that, while early-born afferent neurons connect hair cells to the Mauthner cell, those occurring later only project to the central nucleus [210].



**Figure 5.** Mechanosensory hair cells evolve from single-cell organisms. Choanoflagellate (A,A') are the basis of animals that evolved from a kinocilium surrounded by microvilli into an asymmetric staircase of mechanosensory hair cells (B,C,E) that forms the mechanoelectrical transduction channels (MET) of the lateral line (B,C,C') and vestibular hair cells (E). The lateral line (C,C') and some vestibular hair cells (D) are bipolar, whereas canal cristae and most auditory organs are polarized in 1 direction. Tip links depend on CDH23 and PCDH15 (F) that interact with *Tmc* and others (G) to open up the channel (E') to allow K<sup>+</sup> entrance. Ca<sup>2+</sup> interactions with t ribbons to allow the release of glutamate (E,H). Electoreceptors are unpolarized and resemble Choanoflagellate that either show microvilli (I') or only a central kinocilium (I). Modified after [22,37,47,196,211,212].

The opposing polarity of hair cells and their selective innervation by afferent nerves is determined through the combined action of transcription factor *Emx2* [40,41,213–215]. Ectopic expression of *Emx2* drives all hair cells to organize their kinocilia in a caudal position, while broadly activating the *Notch* pathway results in the inhibition of *Emx2* expression. Thus, all kinocilia are positioned rostrally [40,116,215]. It appears that a

bistable situation then determines of *Emx2* in the rostral sibling through *Notch*-mediated lateral inhibition, which then determines the caudal position for the kinocilium of the rostral sibling and the emergence of the opposing polarity [23].

Auditory hair cells are unipolar in mammals and depend on *Vangl2*, *Dvl1*, *Celsr1* and *Gal2* from the PCP pathway [35,216]. *Emx2* and *Jag1* are both needed for the development of OHCs, which increases the IHC [41,217,218]. Electoreceptors show no polarity in either single kinocilium or multiple microvilli [22] which use nonmechanical sensation [46,219]. Efferents have been found in vertebrates, and vertebrates that receive the vestibular, lateral line and auditory efferents have shown an absence of electoreceptions [193,220].

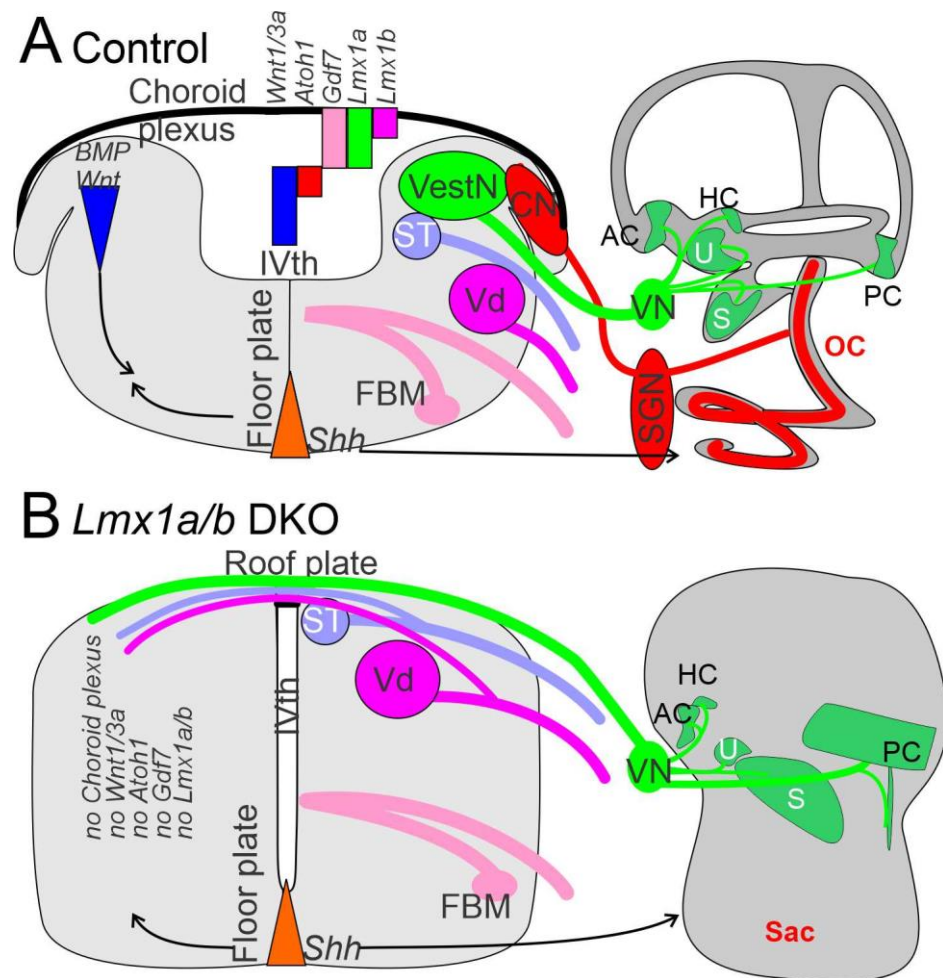
In summary, hair cells evolved from single Choanoflagellate to evolve into *Atoh1* dependent hair cells of vertebrates. Mechanoreception depends on polarity for the inner ear and lateral line, which may counteract of some vestibular and lateral line hair cells or organize unipolarity of canal cristae and most auditory hair cells. Tip links form between stereocilia to open the channel depending on the evolution of *Tmc1/2*. Electoreception does not evolve into mechanotransduction and has no polarity, comparable to Choanoflagellates.

## 5. Conclusions

Choanoflagellates are the basis of animals that evolved approximately 800 million years ago. Apical kinocilia surrounded by microvilli resemble the electoreceptor hair cells, having either a central kinocilium or microvilli [22,23,27]. In contrast, the lateral line, vestibular and cochlear hair cells develop a polarity for a mechanosensory transduction channel for its function [37,44]. *Tmc1* and/or *Tmc2* are an essential connection of mechanotransduction [42], which can be traced to Choanoflagellates [43]. Further work is needed to understand all the functions of various *Tmc* forms. For example, the sequence of mechanosensory hair cells is likely expressed by *Tmc1/2*, which is unique in cyclostomes and splits into two *Tmc* genes in gnathostomes.

The lateral line, ear and electoreception differentiate into hair cells (*Atoh1*) that innervate vestibular neurons (*Neurog1*). In contrast to a simple critical dependency (*Atoh1* define hair cells, *Neurog1* define neurons), centrally nuclei of the brainstem depend on *Atoh1* (LL, ELL, replaced by auditory nuclei in amniotes [26]), *Neurog1/2*, *Olig3*, *Ascl1* and *Ptf1a* (VN; [25]). For the brainstem, *Shh* diffuses from ventral floor plate (Figure 6), whereas the dorsal aspect of the roof plate/choroid plexus depends on *Lmx1a/b*, BMPs and *Wnts* [11,28,153]. In the absence of *Lmx1a/b*, the dorsal formation does not form into a choroid plexus and lacks central nuclei, including *Atoh1* (Figure 6). The reduction of *Shh* and *Gli* may depend on the feedback between the dorsal and ventral interaction with *Lmx1a/b*. A similar interaction between *Shh* defines the cochlear hair cells [173], which interact with *Pax2*, *Lmx1a/b*, *Sox2* and *Gata3* [16,28,58,59] to eliminate cochlear hair cells, suggesting a unique interaction between *Shh* and cochlear development [11,78]. Interestingly enough, the partial formation of some vestibular hair cells in *Shh*, *Pax2*, *Lmx1a/b* and *Gata3* with a near-normal development for central vestibular nuclei (Figure 6) are downstream of *Eya1* [15].

Obviously, there is a formation of the lateral line and electoreception in most vertebrates, whereas amniotes lose the two sensory neurons, brainstem and hair cells, instead evolving an auditory system [26,122]. *Lmx1a/b* null mice showed a loss of cochlear hair cells, cochlear neurons and cochlear nuclei (Figure 6). Unfortunately, the expression of *Lmx1a/b* is required for the dorsal part of the hindbrain, which has not been analyzed in the lateral line and electoreception in gnathostomes. It is possible that the lateral line and electoreception may play a role in *Lmx1a/b* expression to help the transformation of amniotes after the loss of peripheral hair cells and associated nuclei and central projections. Recent evidence has shown that cyclostomes have a different organization of *Lmx* [153], but their expression of *Lmx1a/b* is unclear. Moreover, the two groups of teleosts that have evolved an electoreception have a unique expansion among all gnathostomes [27,135]. This expansion mimics the auditory system of amniotes [26], for which information on *Lmx1a/b* expression is lacking.



**Figure 6.** Central projections of the ear depend on the brainstem. Vestibular neurons project dorsally in the hindbrain in control and *Lmx1a/b* DKO mice (VIII; **A,B**). In *Lmx1a/b* DKO mice, central cochlear projections never develop as they do in controls (**A,B**). In addition, in *Lmx1a/b* DKO mice, vestibular projections interconnect across the roof plate, whereas vestibular fibers are normally separated by the choroid plexus (**A,B**). In addition to the loss of the cochlea and spiral ganglion neurons, the cochlear nucleus does not form in *Lmx1a/b* DKO mice (**B**). Furthermore, in *Lmx1a/b* DKO mice, *Atoh1*, *Gdf7* and *Wnt1/3a* expressions are absent (**A,B**). The signal of *Shh* drives both the ventral brainstem and ventral cochlea (arrows), which are altered without dorsal interaction and lack cochlear neurons in *Lmx1a/b* DKO mice (**A,B**). AC, HC, PC, anterior, horizontal, posterior cristae; CN, cochlear nuclei; FBM, facial branchial motoneurons; S, saccule; SGN, spiral ganglion neurons; ST, solitary tract; U, utricle; Vd, trigeminal; VestN, vestibular nuclei; VN, vestibular neurons. Modified after [11,28,153].

**Funding:** This research was funded by NIH/NIA, grant number R01 AG060504.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** I thank my colleagues for discussing some aspects of the research, particularly V.V. Chizhikov, K.L. Elliott, J. Kersigo, G. Pavlinkova and E.N. Yamoah.

**Conflicts of Interest:** The author declares no conflict of interest.

## References

- Heger, P.; Zheng, W.; Rottmann, A.; Panfilio, K.A.; Wiehe, T. The genetic factors of bilaterian evolution. *eLife* **2020**, *9*, e45530. [[CrossRef](#)] [[PubMed](#)]
- Holland, L. Invertebrate origins of vertebrate nervous systems. In *Evolutionary Neuroscience*; Elsevier: Amsterdam, The Netherlands, 2020; pp. 51–73.
- Chagnaud, B.P.; Engelmann, J.; Fritzsche, B.; Glover, J.C.; Straka, H. Sensing external and self-motion with hair cells: A comparison of the lateral line and vestibular systems from a developmental and evolutionary perspective. *Brain Behav. Evol.* **2017**, *90*, 98–116. [[CrossRef](#)]
- Fritzsche, B.; Elliott, K.L.; Glover, J.C. Gaskell revisited: New insights into spinal autonomic necessitate a revised motor neuron nomenclature. *Cell Tissue Res.* **2017**, *370*, 195–209. [[CrossRef](#)]
- Birmingham, N.A.; Hassan, B.A.; Wang, V.Y.; Fernandez, M.; Banfi, S.; Bellen, H.J.; Fritzsche, B.; Zoghbi, H.Y. Proprioceptor pathway development is dependent on Math1. *Neuron* **2001**, *30*, 411–422. [[CrossRef](#)]
- Kim, K.; Gibboney, S.; Razy-Krajka, F.; Lowe, E.K.; Wang, W.; Stolfi, A. Regulation of neurogenesis by FGF signaling and Neurogenin in the invertebrate chordate *Ciona*. *Front. Cell Dev. Biol.* **2020**, *8*, 477. [[CrossRef](#)]
- Stolfi, A.; Ryan, K.; Meinertzhagen, I.A.; Christiaen, L. Migratory neuronal progenitors arise from the neural plate borders in tunicates. *Nature* **2015**, *527*, 371–374. [[CrossRef](#)] [[PubMed](#)]
- Holland, L.Z.; Daza, D.O. A new look at an old question: When did the second whole genome duplication occur in vertebrate evolution? *Genome Biol.* **2018**, *19*, 1–4. [[CrossRef](#)] [[PubMed](#)]
- Fritzsche, B.; Jahan, I.; Pan, N.; Elliott, K.L. Evolving gene regulatory networks into cellular networks guiding adaptive behavior: An outline how single cells could have evolved into a centralized neurosensory system. *Cell Tissue Res.* **2015**, *359*, 295–313. [[CrossRef](#)] [[PubMed](#)]
- Fritzsche, B.; Elliott, K.L. Gene, cell, and organ multiplication drives inner ear evolution. *Dev. Biol.* **2017**, *431*, 3–15. [[CrossRef](#)]
- Elliott, K.L.; Pavlinková, G.; Chizhikov, V.V.; Yamoah, E.N.; Fritzsche, B. Development in the Mammalian Auditory System Depends on Transcription Factors. *Int. J. Mol. Sci.* **2021**, *22*, 4189. [[CrossRef](#)] [[PubMed](#)]
- Tang, W.J.; Chen, J.S.; Zeller, R.W. Transcriptional regulation of the peripheral nervous system in *Ciona intestinalis*. *Dev. Biol.* **2013**, *378*, 183–193. [[CrossRef](#)]
- Ryan, K.; Lu, Z.; Meinertzhagen, I.A. The peripheral nervous system of the ascidian tadpole larva: Types of neurons and their synaptic networks. *J. Comp. Neurol.* **2018**, *526*, 583–608. [[CrossRef](#)] [[PubMed](#)]
- Manni, L.; Anselmi, C.; Burighel, P.; Martini, M.; Gasparini, F. Differentiation and induced sensorial alteration of the coronal organ in the asexual life of a tunicate. *Integr. Comp. Biol.* **2018**, *58*, 317–328. [[CrossRef](#)]
- Xu, J.; Li, J.; Zhang, T.; Jiang, H.; Ramakrishnan, A.; Fritzsche, B.; Shen, L.; Xu, P.X. Chromatin remodelers and lineage-specific factors interact to target enhancers to establish proneurosensory fate within otic ectoderm. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, 1–12. [[CrossRef](#)]
- Dvorakova, M.; Macova, I.; Bohuslavova, R.; Anderova, M.; Fritzsche, B.; Pavlinkova, G. Early ear neuronal development, but not olfactory or lens development, can proceed without SOX2. *Dev. Biol.* **2020**, *457*, 43–56. [[CrossRef](#)]
- Ma, Q.; Chen, Z.; del Barco Barrantes, I.; de la Pompa, J.L.; Anderson, D.J. Neurogenin1 is essential for the determination of neuronal precursors for proximal cranial sensory ganglia. *Neuron* **1998**, *20*, 469–482. [[CrossRef](#)]
- Kim, W.-Y.; Fritzsche, B.; Serls, A.; Bakel, L.A.; Huang, E.J.; Reichardt, L.F.; Barth, D.S.; Lee, J.E. NeuroD-null mice are deaf due to a severe loss of the inner ear sensory neurons during development. *Development* **2001**, *128*, 417–426. [[CrossRef](#)] [[PubMed](#)]
- Ma, Q.; Anderson, D.J.; Fritzsche, B. Neurogenin 1 null mutant ears develop fewer, morphologically normal hair cells in smaller sensory epithelia devoid of innervation. *J. Assoc. Res. Otolaryngol.* **2000**, *1*, 129–143. [[CrossRef](#)] [[PubMed](#)]
- Jahan, I.; Kersigo, J.; Pan, N.; Fritzsche, B. Neurod1 regulates survival and formation of connections in mouse ear and brain. *Cell Tissue Res.* **2010**, *341*, 95–110. [[CrossRef](#)]
- Macova, I.; Pysanenko, K.; Chumak, T.; Dvorakova, M.; Bohuslavova, R.; Syka, J.; Fritzsche, B.; Pavlinkova, G. Neurod1 is essential for the primary tonotopic organization and related auditory information processing in the midbrain. *J. Neurosci.* **2019**, *39*, 984–1004. [[CrossRef](#)]
- Baker, C.V. The Development and Evolution of Lateral Line Electoreceptors: Insights from Comparative Molecular Approaches. In *Electroreception: Fundamental Insights from Comparative Approaches*; Springer: Berlin/Heidelberg, Germany, 2019; pp. 25–62.
- Elliott, K.L.; Fritzsche, B. Evolution and development of lateral line and electroreception: An integrated perception of neurons, hair cells and brainstem nuclei. In *The Senses*; Fritzsche, B., Bleckmann, H., Eds.; Elsevier: Amsterdam, The Netherlands, 2021; Volume 7, pp. 95–115.
- Lai, H.C.; Seal, R.P.; Johnson, J.E. Making sense out of spinal cord somatosensory development. *Development* **2016**, *143*, 3434–3448. [[CrossRef](#)]
- Hernandez-Miranda, L.R.; Müller, T.; Birchmeier, C. The dorsal spinal cord and hindbrain: From developmental mechanisms to functional circuits. *Dev. Biol.* **2017**, *432*, 34–42. [[CrossRef](#)] [[PubMed](#)]
- Grothe, B.; Carr, C.E.; Casseday, J.H.; Fritzsche, B.; Köppl, C. The evolution of central pathways and their neural processing patterns. In *Evolution of the Vertebrate Auditory System*; Springer: Berlin/Heidelberg, Germany, 2004; pp. 289–359.
- Wullmann, M.F.; Grothe, B. The central nervous organization of the lateral line system. In *The Lateral Line System*; Springer: Berlin/Heidelberg, Germany, 2013; pp. 195–251.

28. Chizhikov, V.V.; Iskusnykh, I.Y.; Fattakhov, N.; Fritzsche, B. Lmx1a and Lmx1b are Redundantly Required for the Development of Multiple Components of the Mammalian Auditory System. *Neuroscience* **2021**, *452*, 247–264. [\[CrossRef\]](#)
29. Lee, K.J.; Dietrich, P.; Jessell, T.M. Genetic ablation reveals that the roof plate is essential for dorsal interneuron specification. *Nature* **2000**, *403*, 734–740. [\[CrossRef\]](#) [\[PubMed\]](#)
30. Pierce, M.L.; Weston, M.D.; Fritzsche, B.; Gabel, H.W.; Ruvkun, G.; Soukup, G.A. MicroRNA—183 family conservation and ciliated neurosensory organ expression. *Evol. Dev.* **2008**, *10*, 106–113. [\[CrossRef\]](#)
31. Nichols, D.H.; Pauley, S.; Jahan, I.; Beisel, K.W.; Millen, K.J.; Fritzsche, B. Lmx1a is required for segregation of sensory epithelia and normal ear histogenesis and morphogenesis. *Cell Tissue Res.* **2008**, *334*, 339–358. [\[CrossRef\]](#)
32. Arendt, D.; Musser, J.M.; Baker, C.V.; Bergman, A.; Cepko, C.; Erwin, D.H.; Pavlicev, M.; Schlosser, G.; Widder, S.; Laubichler, M.D. The origin and evolution of cell types. *Nat. Rev. Genet.* **2016**, *17*, 744–757. [\[CrossRef\]](#)
33. Schlosser, G. A short history of nearly every sense—The evolutionary history of vertebrate sensory cell types. *Integr. Comp. Biol.* **2018**, *58*, 301–316. [\[CrossRef\]](#)
34. Tarchini, B.; Lu, X. New insights into regulation and function of planar polarity in the inner ear. *Neurosci. Lett.* **2019**, *709*, 134373. [\[CrossRef\]](#)
35. Montcouquiol, M.; Rachel, R.A.; Lanford, P.J.; Copeland, N.G.; Jenkins, N.A.; Kelley, M.W. Identification of Vangl2 and Scrb1 as planar polarity genes in mammals. *Nature* **2003**, *423*, 173–177. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Ghimire, S.R.; Deans, M.R. Frizzled3 and Frizzled6 Cooperate with Vangl2 to Direct Cochlear Innervation by type II Spiral Ganglion Neurons. *J. Neurosci.* **2019**, *39*, 8013–8023. [\[CrossRef\]](#)
37. Qiu, X.; Müller, U. Mechanically gated ion channels in mammalian hair cells. *Front. Cell. Neurosci.* **2018**, *12*, 100. [\[CrossRef\]](#)
38. Shibata, S.B.; Ranum, P.T.; Moteki, H.; Pan, B.; Goodwin, A.T.; Goodman, S.S.; Abbas, P.J.; Holt, J.R.; Smith, R.J. RNA interference prevents autosomal-dominant hearing loss. *Am. J. Hum. Genet.* **2016**, *98*, 1101–1113. [\[CrossRef\]](#) [\[PubMed\]](#)
39. Fritzsche, B.; López-Schier, H. Evolution of polarized hair cells in aquatic vertebrates and their connection to directionally sensitive neurons. In *Flow Sensing in Air and Water*; Springer: Berlin/Heidelberg, Germany, 2014; pp. 271–294.
40. Kozak, E.L.; Palit, S.; Miranda-Rodriguez, J.R.; Janjic, A.; Bottcher, A.; Lickert, H.; Enard, W.; Theis, F.J.; Lopez-Schier, H. Epithelial Planar Bipolarity Emerges from Notch-Mediated Asymmetric Inhibition of Emx2. *Curr. Biol.* **2020**, *30*, 1142–1151.e6. [\[CrossRef\]](#) [\[PubMed\]](#)
41. Jiang, T.; Kindt, K.; Wu, D.K. Transcription factor Emx2 controls stereociliary bundle orientation of sensory hair cells. *eLife* **2017**, *6*. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Pan, B.; Akyuz, N.; Liu, X.P.; Asai, Y.; Nist-Lund, C.; Kurima, K.; Derfler, B.H.; Gyorgy, B.; Limapichat, W.; Walujkar, S.; et al. TMC1 Forms the Pore of Mechanosensory Transduction Channels in Vertebrate Inner Ear Hair Cells. *Neuron* **2018**, *99*, 736–753.e6. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Erives, A.; Fritzsche, B. A Screen for Gene Paralogies Delineating Evolutionary Branching Order of Early Metazoa. *G3 Genes Genom. Genet.* **2020**, *10*, 811–826. [\[CrossRef\]](#)
44. Schwander, M.; Kachar, B.; Müller, U. The cell biology of hearing. *J. Cell Biol.* **2010**, *190*, 9–20. [\[CrossRef\]](#)
45. Northcutt, R.G.; Brändle, K.; Fritzsche, B. Electrosensory and mechanosensory lateral line organs arise from single placodes in axolotls. *Dev. Biol.* **1995**, *168*, 358–373. [\[CrossRef\]](#)
46. Leitch, D.B.; Julius, D. Electrosensory Transduction: Comparisons Across Structure, Afferent Response Properties, and Cellular Physiology. In *Electrosensation: Fundamental Insights from Comparative Approaches*; Springer: Berlin/Heidelberg, Germany, 2019; pp. 63–90.
47. Fritzsche, B.; Straka, H. Evolution of vertebrate mechanosensory hair cells and inner ears: Toward identifying stimuli that select mutation driven altered morphologies. *J. Comp. Physiol. A* **2014**, *200*, 5–18. [\[CrossRef\]](#)
48. Xu, P.X.; Adams, J.; Peters, H.; Brown, M.C.; Heaney, S.; Maas, R. Eya1-deficient mice lack ears and kidneys and show abnormal apoptosis of organ primordia. *Nat. Genet.* **1999**, *23*, 113–117. [\[CrossRef\]](#)
49. Zou, D.; Silvius, D.; Fritzsche, B.; Xu, P.-X. Eya1 and Six1 are essential for early steps of sensory neurogenesis in mammalian cranial placodes. *Development* **2004**, *131*, 5561–5572. [\[CrossRef\]](#) [\[PubMed\]](#)
50. Holland, N.D.; Somorjai, I.M. The sensory peripheral nervous system in the tail of a cephalochordate studied by serial blockface scanning electron microscopy. *J. Comp. Neurol.* **2020**, *528*, 2569–2582. [\[CrossRef\]](#) [\[PubMed\]](#)
51. Fritzsche, B.; Northcutt, G. Cranial and spinal nerve organization in amphioxus and lampreys: Evidence for an ancestral craniate pattern. *Cells Tissues Organs* **1993**, *148*, 96–109. [\[CrossRef\]](#)
52. Negrón-Piñero, L.J.; Wu, Y.; Di Gregorio, A. Transcription Factors of the bHLH Family Delineate Vertebrate Landmarks in the Nervous System of a Simple Chordate. *Genes* **2020**, *11*, 1262. [\[CrossRef\]](#)
53. Kageyama, R.; Shimojo, H.; Ohtsuka, T. Dynamic control of neural stem cells by bHLH factors. *Neurosci. Res.* **2019**, *138*, 12–18. [\[CrossRef\]](#)
54. Reiprich, S.; Wegner, M. From CNS stem cells to neurons and glia: Sox for everyone. *Cell Tissue Res.* **2015**, *359*, 111–124. [\[CrossRef\]](#)
55. Riddiford, N.; Schlosser, G. Dissecting the pre-placodal transcriptome to reveal presumptive direct targets of Six1 and Eya1 in cranial placodes. *eLife* **2016**, *5*, e17666. [\[CrossRef\]](#)
56. Millimaki, B.B.; Sweet, E.M.; Riley, B.B. Sox2 is required for maintenance and regeneration, but not initial development, of hair cells in the zebrafish inner ear. *Dev. Biol.* **2010**, *338*, 262–269. [\[CrossRef\]](#) [\[PubMed\]](#)

57. Higuchi, S.; Sugahara, F.; Pascual-Anaya, J.; Takagi, W.; Oisi, Y.; Kuratani, S. Inner ear development in cyclostomes and evolution of the vertebrate semicircular canals. *Nature* **2019**, *565*, 347–350. [[CrossRef](#)] [[PubMed](#)]
58. Bouchard, M.; de Caprona, D.; Busslinger, M.; Xu, P.; Fritzsche, B. Pax2 and Pax8 cooperate in mouse inner ear morphogenesis and innervation. *BMC Dev. Biol.* **2010**, *10*, 89. [[CrossRef](#)] [[PubMed](#)]
59. Duncan, J.S.; Fritzsche, B. Continued expression of GATA3 is necessary for cochlear neurosensory development. *PLoS ONE* **2013**, *8*, e62046. [[CrossRef](#)] [[PubMed](#)]
60. Pirvola, U.; Spencer-Dene, B.; Xing-Qun, L.; Kettunen, P.; Thesleff, I.; Fritzsche, B.; Dickson, C.; Ylikoski, J. FGF/FGFR-2 (IIIb) signaling is essential for inner ear morphogenesis. *J. Neurosci.* **2000**, *20*, 6125–6134. [[CrossRef](#)] [[PubMed](#)]
61. Riccomagno, M.M.; Martinu, L.; Mulheisen, M.; Wu, D.K.; Epstein, D.J. Specification of the mammalian cochlea is dependent on Sonic hedgehog. *Genes Dev.* **2002**, *16*, 2365–2378. [[CrossRef](#)]
62. Kersigo, J.; D'Angelo, A.; Gray, B.D.; Soukup, G.A.; Fritzsche, B. The role of sensory organs and the forebrain for the development of the craniofacial shape as revealed by Foxg1-cre-mediated microRNA loss. *Genesis* **2011**, *49*, 326–341. [[CrossRef](#)] [[PubMed](#)]
63. Pauley, S.; Wright, T.J.; Pirvola, U.; Ornitz, D.; Beisel, K.; Fritzsche, B. Expression and function of FGF10 in mammalian inner ear development. *Dev. Dyn. Off. Publ. Am. Assoc. Anat.* **2003**, *227*, 203–215. [[CrossRef](#)]
64. Pauley, S.; Lai, E.; Fritzsche, B. Foxg1 is required for morphogenesis and histogenesis of the mammalian inner ear. *Dev. Dyn. Off. Publ. Am. Assoc. Anat.* **2006**, *235*, 2470–2482. [[CrossRef](#)]
65. Hwang, C.H.; Simeone, A.; Lai, E.; Wu, D.K. Foxg1 is required for proper separation and formation of sensory cristae during inner ear development. *Dev. Dyn. Off. Publ. Am. Assoc. Anat.* **2009**, *238*, 2725–2734. [[CrossRef](#)]
66. Ma, Q.; Fode, C.; Guillemot, F.; Anderson, D.J. Neurogenin1 and neurogenin2 control two distinct waves of neurogenesis in developing dorsal root ganglia. *Genes Dev.* **1999**, *13*, 1717–1728. [[CrossRef](#)] [[PubMed](#)]
67. Fritzsche, B.; Elliott, K.L.; Pavlinkova, G. Primary sensory map formations reflect unique needs and molecular cues specific to each sensory system. *F1000Research* **2019**, *8*, 345. [[CrossRef](#)]
68. Dennis, D.J.; Han, S.; Schuurmans, C. bHLH transcription factors in neural development, disease, and reprogramming. *Brain Res.* **2019**, *1705*, 48–65. [[CrossRef](#)]
69. Erzurumlu, R.S.; Murakami, Y.; Rijli, F.M. Mapping the face in the somatosensory brainstem. *Nat. Rev. Neurosci.* **2010**, *11*, 252–263. [[CrossRef](#)]
70. Fode, C.; Gradwohl, G.; Morin, X.; Dierich, A.; Le Meur, M.; Goridis, C.; Guillemot, F. The bHLH protein NEUROGENIN 2 is a determination factor for epibranchial placode-derived sensory neurons. *Neuron* **1998**, *20*, 483–494. [[CrossRef](#)]
71. Alsina, B. Mechanisms of cell specification and differentiation in vertebrate cranial sensory systems. *Curr. Opin. Cell Biol.* **2020**, *67*, 79–85. [[CrossRef](#)] [[PubMed](#)]
72. O'Neill, P.; Mak, S.-S.; Fritzsche, B.; Ladher, R.K.; Baker, C.V. The amniote paratympanic organ develops from a previously undiscovered sensory placode. *Nat. Commun.* **2012**, *3*, 1041. [[CrossRef](#)]
73. Sapède, D.; Dyballa, S.; Pujades, C. Cell lineage analysis reveals three different progenitor pools for neurosensory elements in the otic vesicle. *J. Neurosci.* **2012**, *32*, 16424–16434. [[CrossRef](#)] [[PubMed](#)]
74. Moody, S.A.; La Mantia, A.-S. Transcriptional regulation of cranial sensory placode development. In *Current Topics in Developmental Biology*; Elsevier: Amsterdam, The Netherlands, 2015; Volume 111, pp. 301–350.
75. Dykes, I.M.; Tempest, L.; Lee, S.-I.; Turner, E.E. Brn3a and Islet1 act epistatically to regulate the gene expression program of sensory differentiation. *J. Neurosci.* **2011**, *31*, 9789–9799. [[CrossRef](#)]
76. Huang, E.J.; Liu, W.; Fritzsche, B.; Bianchi, L.M.; Reichardt, L.F.; Xiang, M. Brn3a is a transcriptional regulator of soma size, target field innervation and axon pathfinding of inner ear sensory neurons. *Development* **2001**, *128*, 2421–2432. [[CrossRef](#)]
77. Mackowetzky, K.; Yoon, K.H.; Mackowetzky, E.J.; Waskiewicz, A.J. Development and evolution of the vestibular apparatuses of the inner ear. *J. Anat.* **2021**. [[CrossRef](#)]
78. Muthu, V.; Rohacek, A.M.; Yao, Y.; Rakowiecki, S.M.; Brown, A.S.; Zhao, Y.-T.; Meyers, J.; Won, K.-J.; Ramdas, S.; Brown, C.D.; et al. Genomic architecture of Shh-dependent cochlear morphogenesis. *Development* **2019**, *146*, dev181339. [[CrossRef](#)] [[PubMed](#)]
79. Petitpré, C.; Wu, H.; Sharma, A.; Tokarska, A.; Fontanet, P.; Wang, Y.; Helmbacher, F.; Yackle, K.; Silberberg, G.; Hadjab, S. Neuronal heterogeneity and stereotyped connectivity in the auditory afferent system. *Nat. Commun.* **2018**, *9*, 3691. [[CrossRef](#)]
80. Shrestha, B.R.; Chia, C.; Wu, L.; Kujawa, S.G.; Liberman, M.C.; Goodrich, L.V. Sensory neuron diversity in the inner ear is shaped by activity. *Cell* **2018**, *174*, 1229–1246.e17. [[CrossRef](#)] [[PubMed](#)]
81. Sun, S.; Babola, T.; Pregernig, G.; So, K.S.; Nguyen, M.; Su, S.-S.M.; Palermo, A.T.; Bergles, D.E.; Burns, J.C.; Müller, U. Hair cell mechanotransduction regulates spontaneous activity and spiral ganglion subtype specification in the auditory system. *Cell* **2018**, *174*, 1247–1263.e15. [[CrossRef](#)] [[PubMed](#)]
82. Elliott, K.L.; Kersigo, J.M.; Lee, J.H.; Jahan, I.; Pavlinkova, G.; Fritzsche, B.; Yamoah, E.N. Changes in Peripherin-eGFP expression in spiral ganglion neurons; from development to maturity. *Front. Cell. Neurosci.* **2021**, *15*, 181. [[CrossRef](#)]
83. Mao, Y.; Reiprich, S.; Wegner, M.; Fritzsche, B. Targeted deletion of Sox10 by Wnt1-cre defects neuronal migration and projection in the mouse inner ear. *PLoS ONE* **2014**, *9*, e94580. [[CrossRef](#)]
84. Morris, J.K.; Maklad, A.; Hansen, L.A.; Feng, F.; Sorensen, C.; Lee, K.-F.; Macklin, W.B.; Fritzsche, B. A disorganized innervation of the inner ear persists in the absence of ErbB2. *Brain Res.* **2006**, *1091*, 186–199. [[CrossRef](#)] [[PubMed](#)]
85. Freyer, L.; Aggarwal, V.; Morrow, B.E. Dual embryonic origin of the mammalian otic vesicle forming the inner ear. *Development* **2011**, *138*, 5403–5414. [[CrossRef](#)] [[PubMed](#)]

86. Billings, S.E.; Myers, N.M.; Quiruz, L.; Cheng, A.G. Opposing effects of Wnt/ $\beta$ -catenin signaling on epithelial and mesenchymal cell fate in the developing cochlea. *Development* **2021**, *148*, dev199091. [\[CrossRef\]](#)
87. Goodrich, L.V. Early development of the spiral ganglion. In *The Primary Auditory Neurons of the Mammalian Cochlea*; Springer: Berlin/Heidelberg, Germany, 2016; pp. 11–48.
88. Fritzsche, B.; Tessarollo, L.; Coppola, E.; Reichardt, L.F. Neurotrophins in the ear: Their roles in sensory neuron survival and fiber guidance. *Prog. Brain Res.* **2004**, *146*, 265–278. [\[CrossRef\]](#) [\[PubMed\]](#)
89. Bianchi, L.M.; Conover, J.C.; Fritzsche, B.; De Chiara, T.; Lindsay, R.M.; Yancopoulos, G.D. Degeneration of vestibular neurons in late embryogenesis of both heterozygous and homozygous BDNF null mutant mice. *Development* **1996**, *122*, 1965–1973. [\[CrossRef\]](#)
90. Fritzsche, B.; Kersigo, J.; Yang, T.; Jahan, I.; Pan, N. Neurotrophic factor function during ear development: Expression changes define critical phases for neuronal viability. In *The Primary Auditory Neurons of the Mammalian Cochlea*; Dabdoub, A., Fritzsche, B., Popper, A., Fay, R., Eds.; Springer: Berlin/Heidelberg, Germany, 2016; Volume 52, pp. 49–84.
91. Fariñas, I.; Jones, K.R.; Tessarollo, L.; Vigers, A.J.; Huang, E.; Kirstein, M.; De Caprona, D.C.; Coppola, V.; Backus, C.; Reichardt, L.F. Spatial shaping of cochlear innervation by temporally regulated neurotrophin expression. *J. Neurosci.* **2001**, *21*, 6170–6180. [\[CrossRef\]](#) [\[PubMed\]](#)
92. Kersigo, J.; Fritzsche, B. Inner ear hair cells deteriorate in mice engineered to have no or diminished innervation. *Front. Aging Neurosci.* **2015**, *7*, 33. [\[CrossRef\]](#) [\[PubMed\]](#)
93. Fritzsche, B.; Sarai, P.; Barbacid, M.; Silos-Santiago, I. Mice with a targeted disruption of the neurotrophin receptor trkB lose their gustatory ganglion cells early but do develop taste buds. *Int. J. Dev. Neurosci.* **1997**, *15*, 563–576. [\[CrossRef\]](#)
94. Silos-Santiago, I.; Fagan, A.M.; Garber, M.; Fritzsche, B.; Barbacid, M. Severe sensory deficits but normal CNS development in newborn mice lacking TrkB and TrkC tyrosine protein kinase receptors. *Eur. J. Neurosci.* **1997**, *9*, 2045–2056. [\[CrossRef\]](#) [\[PubMed\]](#)
95. Hallböök, F.; Wilson, K.; Thorndyke, M.; Olinski, R.P. Formation and evolution of the chordate neurotrophin and Trk receptor genes. *Brain Behav. Evol.* **2006**, *68*, 133–144. [\[CrossRef\]](#) [\[PubMed\]](#)
96. Bothwell, M. Ngf, bdnf, nt3, and nt4. In *Neurotrophic Factors*; Springer: Berlin/Heidelberg, Germany, 2014; pp. 3–15.
97. Kopecky, B.; Santi, P.; Johnson, S.; Schmitz, H.; Fritzsche, B. Conditional deletion of N-Myc disrupts neurosensory and non-sensory development of the ear. *Dev. Dyn.* **2011**, *240*, 1373–1390. [\[CrossRef\]](#) [\[PubMed\]](#)
98. Schimmang, T.; Pirvola, U. Coupling the cell cycle to development and regeneration of the inner ear. *Semin. Cell Dev. Biol.* **2013**, *24*, 507–513. [\[CrossRef\]](#) [\[PubMed\]](#)
99. Sakamoto, S.; Tateya, T.; Omori, K.; Kageyama, R. Id genes are required for morphogenesis and cellular patterning in the developing mammalian cochlea. *Dev. Biol.* **2020**, *460*, 164–175. [\[CrossRef\]](#)
100. Chen, S.-D.; Yang, J.-L.; Lin, Y.-C.; Chao, A.; Yang, D.-I. Emerging Roles of Inhibitor of Differentiation-1 in Alzheimer's Disease: Cell Cycle Reentry and Beyond. *Cells* **2020**, *9*, 1746. [\[CrossRef\]](#) [\[PubMed\]](#)
101. Baker, N.E.; Brown, N.L. All in the family: Proneural bHLH genes and neuronal diversity. *Development* **2018**, *145*, dev159426. [\[CrossRef\]](#)
102. Pierce, E.T. Histogenesis of the dorsal and ventral cochlear nuclei in the mouse. An autoradiographic study. *J. Comp. Neurol.* **1967**, *131*, 27–53. [\[CrossRef\]](#)
103. Chou, S.-W.; Chen, Z.; Zhu, S.; Davis, R.W.; Hu, J.; Liu, L.; Fernando, C.A.; Kindig, K.; Brown, W.C.; Stepanyan, R. A molecular basis for water motion detection by the mechanosensory lateral line of zebrafish. *Nat. Commun.* **2017**, *8*, 2234. [\[CrossRef\]](#)
104. Altman, J.; Bayer, S.A. *Atlas Of Prenatal Rat Brain Development*; CRC Press: Boca Raton, FL, USA, 1995.
105. Kopecky, B.; Fritzsche, B. The Myc road to hearing restoration. *Cells* **2012**, *1*, 667–698. [\[CrossRef\]](#)
106. Alonso, M.B.D.; Hernandez, I.L.; de la Fuente, M.A.; Garcia-Sancho, J.; Giraldez, F.; Schimmang, T. Transcription factor induced conversion of human fibroblasts towards the hair cell lineage. *PLoS ONE* **2018**, *13*, e0200210.
107. Mantela, J.; Jiang, Z.; Ylikoski, J.; Fritzsche, B.; Zacksenhaus, E.; Pirvola, U. The retinoblastoma gene pathway regulates the postmitotic state of hair cells of the mouse inner ear. *Development* **2005**, *132*, 2377–2388. [\[CrossRef\]](#) [\[PubMed\]](#)
108. Yamoah, E.N.; Li, M.; Shah, A.; Elliott, K.L.; Cheah, K.; Xu, P.X.; Phillips, S.; Young, S.M., Jr.; Eberl, D.F.; Fritzsche, B. Using Sox2 to alleviate the hallmarks of age-related hearing loss. *Ageing Res. Rev.* **2020**, *59*, 101042. [\[CrossRef\]](#) [\[PubMed\]](#)
109. Fritzsche, B.; Gregory, D.; Rosa-Molinar, E. The development of the hindbrain afferent projections in the axolotl: Evidence for timing as a specific mechanism of afferent fiber sorting. *Zoology* **2005**, *108*, 297–306. [\[CrossRef\]](#)
110. Yang, T.; Kersigo, J.; Jahan, I.; Pan, N.; Fritzsche, B. The molecular basis of making spiral ganglion neurons and connecting them to hair cells of the organ of Corti. *Hear. Res.* **2011**, *278*, 21–33. [\[CrossRef\]](#) [\[PubMed\]](#)
111. Pflieger, J.F.; Dubuc, R. Relationship between vestibular primary afferents and vestibulospinal neurons in lampreys. *J. Comp. Neurol.* **2000**, *427*, 255–273. [\[CrossRef\]](#)
112. Duncan, J.S.; Cox, B.C. Anatomy and Development of the Inner Ear. In *The Senses*; Fritzsche, B., Bleckmann, H., Eds.; Elsevier: Amsterdam, The Netherlands, 2020; pp. 253–276.
113. Bell, C.C.; Han, V.; Sawtell, N.B. Cerebellum-like structures and their implications for cerebellar function. *Annu. Rev. Neurosci.* **2008**, *31*, 1–24. [\[CrossRef\]](#) [\[PubMed\]](#)
114. Northcutt, R.G. The phylogenetic distribution and innervation of craniate mechanoreceptive lateral lines. In *The Mechanosensory Lateral Line*; Springer: Berlin/Heidelberg, Germany, 1989; pp. 17–78.
115. Webb, J.F. Morphology of the mechanosensory lateral line system of fishes. In *The Senses*; Fritzsche, B., Bleckmann, H., Eds.; Elsevier: Amsterdam, The Netherlands, 2021; Volume 7, pp. 29–46.

116. Chitnis, A.B. Development of the zebrafish posterior lateral line system. In *The Senses*; Fritzsche, B., Bleckmann, H., Eds.; Elsevier: Amsterdam, The Netherlands, 2021; Volume 7, pp. 66–84.
117. Fritzsche, B.; Beisel, K.; Jones, K.; Farinas, I.; Maklad, A.; Lee, J.; Reichardt, L. Development and evolution of inner ear sensory epithelia and their innervation. *J. Neurobiol.* **2002**, *53*, 143–156. [\[CrossRef\]](#) [\[PubMed\]](#)
118. Pombal, M.A.; Megías, M. Development and functional organization of the cranial nerves in lampreys. *Anat. Rec.* **2019**, *302*, 512–539. [\[CrossRef\]](#)
119. Fritzsche, B. Evolution of the vestibulo-ocular system. *Otolaryngol. Head Neck Surg.* **1998**, *119*, 182–192. [\[CrossRef\]](#)
120. Fritzsche, B.; Signore, M.; Simeone, A. Otx1 null mutant mice show partial segregation of sensory epithelia comparable to lamprey ears. *Dev. Genes Evol.* **2001**, *211*, 388–396. [\[CrossRef\]](#)
121. Fritzsche, B.; Wake, M. The inner ear of gymnophione amphibians and its nerve supply: A comparative study of regressive events in a complex sensory system (Amphibia, Gymnophiona). *Zoomorphology* **1988**, *108*, 201–217. [\[CrossRef\]](#)
122. Fritzsche, B.; Pan, N.; Jahan, I.; Duncan, J.S.; Kopecky, B.J.; Elliott, K.L.; Kersigo, J.; Yang, T. Evolution and development of the tetrapod auditory system: An organ of Corti-centric perspective. *Evol. Dev.* **2013**, *15*, 63–79. [\[CrossRef\]](#)
123. Maklad, A.; Fritzsche, B. Development of vestibular afferent projections into the hindbrain and their central targets. *Brain Res. Bull.* **2003**, *60*, 497–510. [\[CrossRef\]](#)
124. Zecca, A.; Dyballa, S.; Voltes, A.; Bradley, R.; Pujades, C. The order and place of neuronal differentiation establish the topography of sensory projections and the entry points within the hindbrain. *J. Neurosci.* **2015**, *35*, 7475–7486. [\[CrossRef\]](#) [\[PubMed\]](#)
125. Matei, V.; Pauley, S.; Kaing, S.; Rowitch, D.; Beisel, K.; Morris, K.; Feng, F.; Jones, K.; Lee, J.; Fritzsche, B. Smaller inner ear sensory epithelia in Neurog1 null mice are related to earlier hair cell cycle exit. *Dev. Dyn.* **2005**, *234*, 633–650. [\[CrossRef\]](#)
126. Rubel, E.W.; Fritzsche, B. Auditory system development: Primary auditory neurons and their targets. *Annu. Rev. Neurosci.* **2002**, *25*, 51–101. [\[CrossRef\]](#) [\[PubMed\]](#)
127. Ruben, R.J. Development of the inner ear of the mouse: A radioautographic study of terminal mitoses. *Acta Otolaryngol.* **1967**, *220*, 1–44.
128. De No, R.L. *The Primary Acoustic Nuclei*; Raven Press: New York, NY, USA, 1981.
129. Schmidt, H.; Fritzsche, B. Npr2 null mutants show initial overshooting followed by reduction of spiral ganglion axon projections combined with near-normal cochleotopic projection. *Cell Tissue Res.* **2019**, *378*, 15–32. [\[CrossRef\]](#)
130. Elliott, K.L.; Kersigo, J.; Pan, N.; Jahan, I.; Fritzsche, B. Spiral Ganglion Neuron Projection Development to the Hindbrain in Mice Lacking Peripheral and/or Central Target Differentiation. *Front. Neural Circuits* **2017**, *11*, 25. [\[CrossRef\]](#)
131. Fritzsche, B.; Matei, V.; Nichols, D.; Bermingham, N.; Jones, K.; Beisel, K.; Wang, V. Atoh1 null mice show directed afferent fiber growth to undifferentiated ear sensory epithelia followed by incomplete fiber retention. *Dev. Dyn. Off. Publ. Am. Assoc. Anat.* **2005**, *233*, 570–583. [\[CrossRef\]](#) [\[PubMed\]](#)
132. Milinkeviciute, G.; Cramer, K.S. Development of the ascending auditory pathway. In *The Senses*; Fritzsche, B., Bleckmann, H., Eds.; Elsevier: Amsterdam, The Netherlands, 2021; Volume 2, pp. 337–353.
133. Duncan, J.S.; Fritzsche, B.; Houston, D.W.; Ketchum, E.M.; Kersigo, J.; Deans, M.R.; Elliott, K.L. Topologically correct central projections of tetrapod inner ear afferents require Fzd3. *Sci. Rep.* **2019**, *9*, 10298. [\[CrossRef\]](#) [\[PubMed\]](#)
134. Maklad, A.; Kamel, S.; Wong, E.; Fritzsche, B. Development and organization of polarity-specific segregation of primary vestibular afferent fibers in mice. *Cell Tissue Res.* **2010**, *340*, 303–321. [\[CrossRef\]](#) [\[PubMed\]](#)
135. Bell, C.C.; Maler, L. Central neuroanatomy of electrosensory systems in fish. In *Electroreception*; Springer: Berlin/Heidelberg, Germany, 2005; pp. 68–111.
136. Millimaki, B.B.; Sweet, E.M.; Dhasan, M.S.; Riley, B.B. Zebrafish atoh1 genes: Classic proneural activity in the inner ear and regulation by Fgf and Notch. *Development* **2007**, *134*, 295–305. [\[CrossRef\]](#)
137. Northcutt, R.G. Distribution and innervation of lateral line organs in the axolotl. *J. Comp. Neurol.* **1992**, *325*, 95–123. [\[CrossRef\]](#)
138. Pan, N.; Jahan, I.; Kersigo, J.; Duncan, J.S.; Kopecky, B.; Fritzsche, B. A novel Atoh1 “self-terminating” mouse model reveals the necessity of proper Atoh1 level and duration for hair cell differentiation and viability. *PLoS ONE* **2012**, *7*, e30358. [\[CrossRef\]](#)
139. Xiang, M.; Maklad, A.; Pirvola, U.; Fritzsche, B. Brn3c null mutant mice show long-term, incomplete retention of some afferent inner ear innervation. *BMC Neurosci.* **2003**, *4*, 2. [\[CrossRef\]](#)
140. Nieuwenhuys, R.; Puelles, L. *Towards a New Neuromorphology*; Springer: Berlin/Heidelberg, Germany, 2015.
141. Watson, C.; Shimogori, T.; Puelles, L. Mouse Fgf8-Cre-LacZ lineage analysis defines the territory of the postnatal mammalian isthmus. *J. Comp. Neurol.* **2017**, *525*, 2782–2799. [\[CrossRef\]](#)
142. Iskusnykh, I.Y.; Steshina, E.Y.; Chizhikov, V.V. Loss of Ptf1a leads to a widespread cell-fate misspecification in the brainstem, affecting the development of somatosensory and viscerosensory nuclei. *J. Neurosci.* **2016**, *36*, 2691–2710. [\[CrossRef\]](#)
143. Yamada, M.; Seto, Y.; Taya, S.; Owa, T.; Inoue, Y.U.; Inoue, T.; Kawaguchi, Y.; Nabeshima, Y.-i.; Hoshino, M. Specification of spatial identities of cerebellar neuron progenitors by ptf1a and atoh1 for proper production of GABAergic and glutamatergic neurons. *J. Neurosci.* **2014**, *34*, 4786–4800. [\[CrossRef\]](#) [\[PubMed\]](#)
144. Fujiyama, T.; Yamada, M.; Terao, M.; Terashima, T.; Hioki, H.; Inoue, Y.U.; Inoue, T.; Masuyama, N.; Obata, K.; Yanagawa, Y. Inhibitory and excitatory subtypes of cochlear nucleus neurons are defined by distinct bHLH transcription factors, Ptf1a and Atoh1. *Development* **2009**, *136*, 2049–2058. [\[CrossRef\]](#) [\[PubMed\]](#)
145. Lowenstein, E.D.; Rusanova, A.; Stelzer, J.; Hernaiz-Llorens, M.; Schroer, A.E.; Epifanova, E.; Bladt, F.; Isik, E.G.; Buchert, S.; Jia, S.; et al. Olig3 regulates early cerebellar development. *eLife* **2021**, *10*. [\[CrossRef\]](#) [\[PubMed\]](#)

146. Sankar, S.; Yellajoshyula, D.; Zhang, B.; Teets, B.; Rockweiler, N.; Kroll, K.L. Gene regulatory networks in neural cell fate acquisition from genome-wide chromatin association of Geminin and Zic1. *Sci. Rep.* **2016**, *6*, 37412. [\[CrossRef\]](#)
147. Lee, H.-K.; Lee, H.-S.; Moody, S.A. Neural transcription factors: From embryos to neural stem cells. *Mol. Cells* **2014**, *37*, 705. [\[CrossRef\]](#)
148. Aruga, J.; Hatayama, M. Comparative genomics of the Zic family genes. In *Zic Family*; Springer: Berlin/Heidelberg, Germany, 2018; pp. 3–26.
149. Merzdorf, C.S.; Sive, H.L. The zic1 gene is an activator of Wnt signaling. *Int. J. Dev. Biol.* **2004**, *50*, 611–617. [\[CrossRef\]](#)
150. Merzdorf, C.; Forecki, J. Amphibian Zic Genes. In *Zic Family*; Springer: Berlin/Heidelberg, Germany, 2018; pp. 107–140.
151. Litingtung, Y.; Dahn, R.D.; Li, Y.; Fallon, J.F.; Chiang, C. Shh and Gli3 are dispensable for limb skeleton formation but regulate digit number and identity. *Nature* **2002**, *418*, 979–983. [\[CrossRef\]](#)
152. Jahan, I.; Kersigo, J.; Elliott, K.L.; Fritzsche, B. Smoothed overexpression causes trochlear motoneurons to reroute and innervate ipsilateral eyes. *Cell Tissue Res.* **2021**, *384*, 59–72. [\[CrossRef\]](#)
153. Glover, J.C.; Elliott, K.L.; Erives, A.; Chizhikov, V.V.; Fritzsche, B. Wilhelm His' lasting insights into hindbrain and cranial ganglia development and evolution. *Dev. Biol.* **2018**, *444*, S14–S24. [\[CrossRef\]](#) [\[PubMed\]](#)
154. Mishima, Y.; Lindgren, A.G.; Chizhikov, V.V.; Johnson, R.L.; Millen, K.J. Overlapping function of Lmx1a and Lmx1b in anterior hindbrain roof plate formation and cerebellar growth. *J. Neurosci.* **2009**, *29*, 11377–11384. [\[CrossRef\]](#)
155. Zhang, T.; Xu, J.; Xu, P.X. Eya2 expression during mouse embryonic development revealed by Eya2(lacZ) knockin reporter and homozygous mice show mild hearing loss. *Dev. Dyn. Off. Publ. Am. Assoc. Anat.* **2021**. [\[CrossRef\]](#)
156. Fritzsche, B.; Pauley, S.; Feng, F.; Matei, V.; Nichols, D. The molecular and developmental basis of the evolution of the vertebrate auditory system. *Int. J. Comp. Psychol.* **2006**, *19*, 1–25.
157. Pan, N.; Jahan, I.; Lee, J.E.; Fritzsche, B. Defects in the cerebella of conditional Neurod1 null mice correlate with effective Tg (Atoh1-cre) recombination and granule cell requirements for Neurod1 for differentiation. *Cell Tissue Res.* **2009**, *337*, 407–428. [\[CrossRef\]](#) [\[PubMed\]](#)
158. Wang, V.Y.; Rose, M.F.; Zoghbi, H.Y. Math1 expression redefines the rhombic lip derivatives and reveals novel lineages within the brainstem and cerebellum. *Neuron* **2005**, *48*, 31–43. [\[CrossRef\]](#)
159. Storm, R.; Cholewa-Waclaw, J.; Reuter, K.; Bröhl, D.; Sieber, M.; Treier, M.; Müller, T.; Birchmeier, C. The bHLH transcription factor Olig3 marks the dorsal neuroepithelium of the hindbrain and is essential for the development of brainstem nuclei. *Development* **2009**, *136*, 295–305. [\[CrossRef\]](#)
160. Imayoshi, I.; Kageyama, R. bHLH factors in self-renewal, multipotency, and fate choice of neural progenitor cells. *Neuron* **2014**, *82*, 9–23. [\[CrossRef\]](#)
161. Jahan, I.; Pan, N.; Elliott, K.L.; Fritzsche, B. The quest for restoring hearing: Understanding ear development more completely. *Bioessays* **2015**, *37*, 1016–1027. [\[CrossRef\]](#)
162. Kersigo, J.; Gu, L.; Xu, L.; Pan, N.; Vijayakuma, S.; Jones, T.; Shibata, S.B.; Fritzsche, B.; Hansen, M.R. Effects of Neurod1 Expression on Mouse and Human Schwannoma Cells. *Laryngoscope* **2021**, *131*, E259–E270. [\[CrossRef\]](#)
163. Fritzsche, B.; Sonntag, R.; Dubuc, R.; Ohta, Y.; Grillner, S. Organization of the six motor nuclei innervating the ocular muscles in lamprey. *J. Comp. Neurol.* **1990**, *294*, 491–506. [\[CrossRef\]](#) [\[PubMed\]](#)
164. Oury, F.; Murakami, Y.; Renaud, J.-S.; Pasqualetti, M.; Charnay, P.; Ren, S.-Y.; Rijli, F.M. Hoxa2-and rhombomere-dependent development of the mouse facial somatosensory map. *Science* **2006**, *313*, 1408–1413. [\[CrossRef\]](#) [\[PubMed\]](#)
165. Abaira, V.E.; Ginty, D.D. The sensory neurons of touch. *Neuron* **2013**, *79*, 618–639. [\[CrossRef\]](#)
166. Bermingham, N.A.; Hassan, B.A.; Price, S.D.; Vollrath, M.A.; Ben-Arie, N.; Eatock, R.A.; Bellen, H.J.; Lysakowski, A.; Zoghbi, H.Y. Math1: An essential gene for the generation of inner ear hair cells. *Science* **1999**, *284*, 1837–1841. [\[CrossRef\]](#)
167. Maricich, S.M.; Xia, A.; Mathes, E.L.; Wang, V.Y.; Oghalai, J.S.; Fritzsche, B.; Zoghbi, H.Y. Atoh1-lineal neurons are required for hearing and for the survival of neurons in the spiral ganglion and brainstem accessory auditory nuclei. *J. Neurosci.* **2009**, *29*, 11123–11133. [\[CrossRef\]](#)
168. Birol, O.; Ohyama, T.; Edlund, R.K.; Drakou, K.; Georgiades, P.; Groves, A.K. The mouse Foxi3 transcription factor is necessary for the development of posterior placodes. *Dev. Biol.* **2016**, *409*, 139–151. [\[CrossRef\]](#)
169. Wright, T.J.; Mansour, S.L. Fgf3 and Fgf10 are required for mouse otic placode induction. *Development* **2003**, *130*, 3379–3390. [\[CrossRef\]](#)
170. Urness, L.D.; Paxton, C.N.; Wang, X.; Schoenwolf, G.C.; Mansour, S.L. FGF signaling regulates otic placode induction and refinement by controlling both ectodermal target genes and hindbrain Wnt8a. *Dev. Biol.* **2010**, *340*, 595–604. [\[CrossRef\]](#)
171. Ahmed, M.; Xu, J.; Xu, P.-X. EYA1 and SIX1 drive the neuronal developmental program in cooperation with the SWI/SNF chromatin-remodeling complex and SOX2 in the mammalian inner ear. *Development* **2012**, *139*, 1965–1977. [\[CrossRef\]](#) [\[PubMed\]](#)
172. Burton, Q.; Cole, L.K.; Mulheisen, M.; Chang, W.; Wu, D.K. The role of Pax2 in mouse inner ear development. *Dev. Biol.* **2004**, *272*, 161–175. [\[CrossRef\]](#) [\[PubMed\]](#)
173. Riccomagno, M.M.; Takada, S.; Epstein, D.J. Wnt-dependent regulation of inner ear morphogenesis is balanced by the opposing and supporting roles of Shh. *Genes Dev.* **2005**, *19*, 1612–1623. [\[CrossRef\]](#)
174. Ohyama, T.; Basch, M.L.; Mishina, Y.; Lyons, K.M.; Segil, N.; Groves, A.K. BMP signaling is necessary for patterning the sensory and nonsensory regions of the developing mammalian cochlea. *J. Neurosci. Off. J. Soc. Neurosci.* **2010**, *30*, 15044–15051. [\[CrossRef\]](#)

175. Chang, W.; Lin, Z.; Kulesa, H.; Hebert, J.; Hogan, B.L.; Wu, D.K. Bmp4 is essential for the formation of the vestibular apparatus that detects angular head movements. *PLoS Genet.* **2008**, *4*, e1000050. [\[CrossRef\]](#)
176. Munnamalai, V.; Fekete, D.M. Wnt signaling during cochlear development. *Semin. Cell Dev. Biol.* **2013**, *24*, 480–489. [\[CrossRef\]](#) [\[PubMed\]](#)
177. Wright, K.D.; Rogers, A.A.M.; Zhang, J.; Shim, K. Cooperative and independent functions of FGF and Wnt signaling during early inner ear development. *BMC Dev. Biol.* **2015**, *15*, 1–15. [\[CrossRef\]](#)
178. Sienknecht, U.J.; Fekete, D.M. Mapping of Wnt, frizzled, and Wnt inhibitor gene expression domains in the avian otic primordium. *J. Comp. Neurol.* **2009**, *517*, 751–764. [\[CrossRef\]](#)
179. Tambalo, M.; Anwar, M.; Ahmed, M.; Streit, A. Enhancer activation by FGF signalling during otic induction. *Dev. Biol.* **2020**, *457*, 69–82. [\[CrossRef\]](#) [\[PubMed\]](#)
180. Fekete, D.M.; Wu, D.K. Revisiting cell fate specification in the inner ear. *Curr. Opin. Neurobiol.* **2002**, *12*, 35–42. [\[CrossRef\]](#)
181. Groves, A.K.; Fekete, D.M. Shaping sound in space: The regulation of inner ear patterning. *Development* **2012**, *139*, 245–257. [\[CrossRef\]](#)
182. Kiernan, A.E.; Pelling, A.L.; Leung, K.K.; Tang, A.S.; Bell, D.M.; Tease, C.; Lovell-Badge, R.; Steel, K.P.; Cheah, K.S. Sox2 is required for sensory organ development in the mammalian inner ear. *Nature* **2005**, *434*, 1031–1035. [\[CrossRef\]](#) [\[PubMed\]](#)
183. Filova, I.; Dvorakova, M.; Bohuslavova, R.; Pavlinek, A.; Elliott, K.L.; Vochyanova, S.; Fritzsche, B.; Pavlinkova, G. Combined Atoh1 and Neurod1 Deletion Reveals Autonomous Growth of Auditory Nerve Fibers. *Mol. Neurobiol.* **2020**, *57*, 5307–5323. [\[CrossRef\]](#)
184. Hertzano, R.; Montcouquiol, M.; Rashi-Elkeles, S.; Elkon, R.; Yucel, R.; Frankel, W.N.; Rechavi, G.; Moroy, T.; Friedman, T.B.; Kelley, M.W.; et al. Transcription profiling of inner ears from Pou4f3(ddl/ddl) identifies Gfi1 as a target of the Pou4f3 deafness gene. *Hum. Mol. Genet.* **2004**, *13*, 2143–2153. [\[CrossRef\]](#)
185. Li, J.; Zhang, T.; Ramakrishnan, A.; Fritzsche, B.; Xu, J.; Wong, E.Y.M.; Loh, Y.E.; Ding, J.; Shen, L.; Xu, P.X. Dynamic changes in cis-regulatory occupancy by Six1 and its cooperative interactions with distinct cofactors drive lineage-specific gene expression programs during progressive differentiation of the auditory sensory epithelium. *Nucleic Acids Res.* **2020**, *48*, 2880–2896. [\[CrossRef\]](#)
186. Wallis, D.; Hamblen, M.; Zhou, Y.; Venken, K.J.; Schumacher, A.; Grimes, H.L.; Zoghbi, H.Y.; Orkin, S.H.; Bellen, H.J. The zinc finger transcription factor Gfi1, implicated in lymphomagenesis, is required for inner ear hair cell differentiation and survival. *Development* **2003**, *130*, 221–232. [\[CrossRef\]](#) [\[PubMed\]](#)
187. Nakano, Y.; Jahan, I.; Bonde, G.; Sun, X.; Hildebrand, M.S.; Engelhardt, J.F.; Smith, R.J.; Cornell, R.A.; Fritzsche, B.; Bánfi, B. A mutation in the Srrm4 gene causes alternative splicing defects and deafness in the Bronx waltzer mouse. *PLoS Genet.* **2012**, *8*, e1002966. [\[CrossRef\]](#)
188. Nakano, Y.; Wiechert, S.; Fritzsche, B.; Bánfi, B. Inhibition of a transcriptional repressor rescues hearing in a splicing factor-deficient mouse. *Life Sci. Alliance* **2020**, *3*, e202000841. [\[CrossRef\]](#) [\[PubMed\]](#)
189. Bulfone, A.; Menguzzato, E.; Broccoli, V.; Marchitelli, A.; Gattuso, C.; Mariani, M.; Consalez, G.G.; Martinez, S.; Ballabio, A.; Bánfi, B. Barhl1, a gene belonging to a new subfamily of mammalian homeobox genes, is expressed in migrating neurons of the CNS. *Hum. Mol. Genet.* **2000**, *9*, 1443–1452. [\[CrossRef\]](#)
190. Chellappa, R.; Li, S.; Pauley, S.; Jahan, I.; Jin, K.; Xiang, M. Barhl1 regulatory sequences required for cell-specific gene expression and autoregulation in the inner ear and central nervous system. *Mol. Cell. Biol.* **2008**, *28*, 1905–1914. [\[CrossRef\]](#) [\[PubMed\]](#)
191. Lewis, E.R.; Leverenz, E.L.; Bialek, W.S. *The Vertebrate Inner Ear*; CRC Press: Boca Raton, FL, USA, 1985; p. 248.
192. Lysakowski, A. Anatomy and microstructural organization of vestibular hair cells. In *The Senses*; Fritzsche, B., Bleckmann, H., Eds.; Elsevier: Amsterdam, The Netherlands, 2021; Volume 6, pp. 173–184.
193. Fritzsche, B.; Elliott, K.L. Evolution and Development of the Inner Ear Efferent System: Transforming a Motor Neuron Population to Connect to the Most Unusual Motor Protein via Ancient Nicotinic Receptors. *Front. Cell Neurosci.* **2017**, *11*, 114. [\[CrossRef\]](#)
194. Eatock, R.A.; Rusch, A.; Lysakowski, A.; Saeki, M. Hair cells in mammalian utricles. *Otolaryngol. Head Neck Surg.* **1998**, *119*, 172–181. [\[CrossRef\]](#)
195. Platt, C.; Straka, H. Vestibular endorgans in vertebrates and adequate sensory stimuli. In *The Senses*; Fritzsche, B., Bleckmann, H., Eds.; Elsevier: Amsterdam, The Netherlands, 2021; Volume 6, pp. 108–128.
196. Curthoys, I.S. The anatomical and physiological basis of clinical tests of otolith function. A tribute to Yoshio Uchino. *Front. Neurol.* **2020**, *11*, 566895. [\[CrossRef\]](#)
197. Elliott, K.L.; Fritzsche, B.; Duncan, J.S. Evolutionary and Developmental Biology Provide Insights Into the Regeneration of Organ of Corti Hair Cells. *Front. Cell. Neurosci.* **2018**, *12*, 252. [\[CrossRef\]](#) [\[PubMed\]](#)
198. Hudspeth, A.J. How the ear's works work. *Nature* **1989**, *341*, 397–404. [\[CrossRef\]](#) [\[PubMed\]](#)
199. Pan, B.; Géléc, G.S.; Asai, Y.; Horwitz, G.C.; Kurima, K.; Ishikawa, K.; Kawashima, Y.; Griffith, A.J.; Holt, J.R. TMC1 and TMC2 are components of the mechanotransduction channel in hair cells of the mammalian inner ear. *Neuron* **2013**, *79*, 504–515. [\[CrossRef\]](#) [\[PubMed\]](#)
200. Duncan, J.S.; Stoller, M.L.; Francl, A.F.; Tissir, F.; Devenport, D.; Deans, M.R. Celsr1 coordinates the planar polarity of vestibular hair cells during inner ear development. *Dev. Biol.* **2017**, *423*, 126–137. [\[CrossRef\]](#) [\[PubMed\]](#)
201. Ratzan, E.M.; Moon, A.M.; Deans, M.R. Fgf8 genetic labeling reveals the early specification of vestibular hair cell type in mouse utricle. *Development* **2020**, *147*. [\[CrossRef\]](#)

202. Ketchum, E.M.; Sheltz-Kemp, S.N.; Duncan, J.S. Molecular basis of vestibular organ formation during ontogeny. In *The Senses*; Fritzsche, B., Bleckmann, H., Eds.; Elsevier: Amsterdam, The Netherlands, 2021; Volume 6, pp. 129–144.
203. Deans, M.R. A balance of form and function: Planar polarity and development of the vestibular maculae. *Semin. Cell Dev. Biol.* **2013**, *24*, 490–498. [[CrossRef](#)] [[PubMed](#)]
204. Ono, K.; Keller, J.; Ramírez, O.L.; Garrido, A.G.; Zobeiri, O.A.; Chang, H.H.V.; Vijayakumar, S.; Ayiotis, A.; Duester, G.; Della Santina, C.C. Retinoic acid degradation shapes zonal development of vestibular organs and sensitivity to transient linear accelerations. *Nat. Commun.* **2020**, *11*, 63. [[CrossRef](#)]
205. Balmer, T.S.; Trussell, L.O. Selective targeting of unipolar brush cell subtypes by cerebellar mossy fibers. *eLife* **2019**, *8*, e44964. [[CrossRef](#)]
206. Bleckmann, H. Central lateral line pathways and central integration of lateral line information. In *The Senses*; Fritzsche, B., Bleckmann, H., Eds.; Elsevier: Amsterdam, The Netherlands, 2021; Volume 7, pp. 163–184.
207. Nicolson, T. The genetics of hair-cell function in zebrafish. *J. Neurogenet.* **2017**, *31*, 102–112. [[CrossRef](#)]
208. Krey, J.F.; Chatterjee, P.; Dumont, R.A.; O’Sullivan, M.; Choi, D.; Bird, J.E.; Barr-Gillespie, P.G. Mechanotransduction-dependent control of stereocilia dimensions and row identity in inner hair cells. *Curr. Biol.* **2020**, *30*, 442–454.e7. [[CrossRef](#)]
209. Vischer, H.A. The development of lateral-line receptors in *Eigenmannia* (Teleostei, Gymnotiformes). I. The mechanoreceptive lateral-line system (Part 1 of 2). *Brain Behav. Evol.* **1989**, *33*, 205–213. [[CrossRef](#)] [[PubMed](#)]
210. Pujol-Martí, J.; Zecca, A.; Baudoin, J.P.; Faucherre, A.; Asakawa, K.; Kawakami, K.; López-Schier, H. Neuronal birth order identifies a dimorphic sensorineural map. *J. Neurosci. Off. J. Soc. Neurosci.* **2012**, *32*, 2976–2987. [[CrossRef](#)]
211. Fattal, D.; Hansen, M.; Fritzsche, B. Aging-related balance impairment and hearing loss. In *The Wiley Handbook on the Aging Mind and Brain*; John Wiley & Sons: Hoboken, NJ, USA, 2018; pp. 315–336.
212. Engelmann, J.; Fritzsche, B. Lateral line input to ‘almost’ all vertebrates shares a common organization with different distinct connections. In *The Evolution Of Sensory System Revealed: Gene Regulation, Cellular Networks And Processes*; Fritzsche, B., Elliott, K.L., Hall, B., Moody, S., Eds.; Wiley: Hoboken, NJ, USA, 2021.
213. Jacobo, A.; Dasgupta, A.; Erzberger, A.; Siletti, K.; Hudspeth, A.J. Notch-Mediated Determination of Hair-Bundle Polarity in Mechanosensory Hair Cells of the Zebrafish Lateral Line. *Curr. Biol.* **2019**, *29*, 3579–3587.e7. [[CrossRef](#)] [[PubMed](#)]
214. Ji, Y.R.; Warrier, S.; Jiang, T.; Wu, D.K.; Kindt, K.S. Directional selectivity of afferent neurons in zebrafish neuromasts is regulated by Emx2 in presynaptic hair cells. *eLife* **2018**, *7*. [[CrossRef](#)] [[PubMed](#)]
215. Ohta, S.; Ji, Y.R.; Martin, D.; Wu, D.K. Emx2 regulates hair cell rearrangement but not positional identity within neuromasts. *eLife* **2020**, *9*, e60432. [[CrossRef](#)]
216. Tarchini, B.; Jolicœur, C.; Cayouette, M. A molecular blueprint at the apical surface establishes planar asymmetry in cochlear hair cells. *Dev. Cell* **2013**, *27*, 88–102. [[CrossRef](#)]
217. Kimura, J.; Suda, Y.; Kurokawa, D.; Hossain, Z.M.; Nakamura, M.; Takahashi, M.; Hara, A.; Aizawa, S. Emx2 and Pax6 function in cooperation with Otx2 and Otx1 to develop caudal forebrain primordium that includes future archipallium. *J. Neurosci. Off. J. Soc. Neurosci.* **2005**, *25*, 5097–5108. [[CrossRef](#)]
218. Holley, M.; Rhodes, C.; Kneebone, A.; Herde, M.K.; Fleming, M.; Steel, K.P. Emx2 and early hair cell development in the mouse inner ear. *Dev. Biol.* **2010**, *340*, 547–556. [[CrossRef](#)]
219. Bellono, N.W.; Leitch, D.B.; Julius, D. Molecular tuning of electroreception in sharks and skates. *Nature* **2018**, *558*, 122–126. [[CrossRef](#)]
220. Simmons, D.; Duncan, J.; de Caprona, D.C.; Fritzsche, B. Development of the inner ear efferent system. In *Auditory and Vestibular Efferents*; Springer: Berlin/Heidelberg, Germany, 2011; pp. 187–216.