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# The Molecular Mechanisms Driving Placode Development; A Multifaceted Process Driven by Complex Signaling Pathways: A Review

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***Abstract:*** **Placodes, specialized thickened areas of the ectoderm, give rise to both sensory and non-sensory structures. Placode induction and differentiation is a multi-step process involving interactions between several organs and signaling pathways. These placodes develop from the pre-placodal region, which encircles the cranial part of the neural plate. They are induced by FGF signaling and inhibited by Wnt and Bmp pathways. Vital sensory organs like the olfactory epithelium, inner ear, and eye lens are formed because of FGF signaling, which is critical for supporting the specification of diverse placodal progenitors. Different placodal types are differentiated simultaneously by regulating the Wnt and BMP pathways, creating epithelial structures like hair, teeth, and breasts. In addition to being essential to developmental biology, understanding the precise molecular mechanisms driving placode induction and differentiation has important implications for research in regenerative medicine and evolution. Further investigation could reveal new information about the complex mechanisms that control tissue specialization and functional variety in vertebrate species.**

***Keywords:*** **Placodes, pre-placodal region, neural tube, progenitors, regenerative medicine.**

## 1. INTRODUCTION

The development of the sensory systems in our body relies on the interactions among ectodermal cells, which communicate through contact and molecular signals. These interactions guide the formation of sophisticated sensory organs through complex and integrated processes [1]. The organs of vision, hearing, smell, and even the skin's hair originate from basic thickenings on the ectoderm known as placodes. These placodes and the skin's outer layer (epidermis) develop from the ectoderm that doesn't form the nervous system, unlike the neural ectoderm, which transforms into the peripheral and central nervous systems. These non-neural ectodermal placodes are formed due to interactions with neighboring cells and tissues from the neural plate ectoderm, endoderm, and mesoderm. The specific interactions vary depending on the type of placode **[2].**

In the head, sensory placodes develop into several vital structures, including the adenohypophysis, the olfactive epithelium that covers the nasal cavity, the eye lens, the labyrinthine inner ear containing the cochleovestibular ganglion, and the peripheral parts of the cranial sensory ganglia **[3, 4].** The non-neuronal non-sensory placodes give rise to the epithelium of the oral cavity, which is crucial for teeth development, as well as various dermal structures found throughout the body, including hair, mammary glands, and sweat glands **[5].** Placode formation has helped researchers understand the physiological and molecular mechanisms driving sensory abnormalities and craniofacial morphogenesis. **[6].**

## 2. HISTORICAL VIEW ON THE DEVELOPMENT OF PLACODES

The recognition of placodes dates to the late 19th century **[7, 8].** Pioneering contributions were made by **[9-11]** providing crucial initial explanations of placode position, early neurogenesis, and the sensory inputs influenced by placodes and neural crest cells in many species. These studies have aimed to uncover both similarities and differences between species **[12, 13].**

During the early half of the twentieth century, sensory neurogenic placode research in mammals was particularly controversial. Opposing reports created a challenge in establishing a definitive consensus on whether the ganglia of cranial nerves uniquely originated from the neural crest or if the surface ectodermal cells also played a role. Batten effectively reviewed this debate as he established his histologic explanations of the development of the trigeminal placode in sheep **[14].** This observation aligns with later descriptions, which were confirmed using markers specific to the trigeminal placode, such as Pax3 and Fgfr4 **[15].**

Significant improvement has been made in elucidating the mechanisms directing placode formation. Although early studies primarily concentrated on amphibians, the original fate maps from researchers laid the groundwork for understanding placode development **[16, 17].**

In the early 1990s, the availability of specific markers enabled experimental studies in chicks to address fundamental questions about the fate of the placodes. The identification of Pax3 as a biomarker for the ophthalmic trigeminal placodes, as demonstrated in the study by **[15],** highlighted a significant advancement. These studies helped to answer essential questions related to placode induction, competence, specification, and commitment toward specific placodal fates **[18-20].**

## 3. DERIVATIVES OF CRANIAL PLACODES AND THEIR FUNCTION

With contributions from the cells in the cranial part of the neural crest, cranial placodes significantly generate sensory neurons responsible for hearing, balance, smell, taste, pain, temperature, touch sensation, and even blood pressure. The cranial neural crest, on the other hand, contributes to all the glia and proximal portions of the sensory ganglia. **[2].** The placodes located at the developing head region can be categorized into three groups:

**A. The anterior cranial placodes consist of adenohypophysis, olfactive, and eye-lens placodes.**

Rathke's pouch is formed when the adenohypophysis forming placode invaginates from the upper part of the mouth. This pouch then divides into the anterior pituitary, which produces a total of five types of neuroendocrine hormone-discharging cells **[21].**

The lens placode undergoes invagination, forming the lens vesicle, which eventually develops into the lens of the eye. Unlike other cranial placodes, the adenohypophysis-forming placode and eye-lens placodes do not give rise to sensory neurons; all other placodes in the head generate sensory neurons **[22].**

The olfactive placode developed next to the forebrain in the anterior region. It generates odorant and pheromone receptors, which continue to the olfactory bulb. Furthermore, the olfactive placode generates supporting cells and neurons that express GnRH. These neurons migrate into the central nervous system (CNS) via the olfactory nerve. **[23].**

**B. The posterior placodes include the lateral line, otic, and epibranchial placodes.**

These placodes respectively generate the lateral line system (found in fishes and amphibians), labyrinthine (inner) ear, and distal part of the geniculate, petrosal, and nodose ganglia sensory neurons **[24].**

The otic placode folds inwards and detaches from the outer layer of cells, forming the otic vesicle. This vesicle then develops into the inner ear's cochlear and vestibular systems, along with the sensory neurons found in the nearby vestibulocochlear ganglion **[25].**

The epibranchial placodes have three types: geniculate, petrosal, and nodose. These placodes manage the development of the distal parts of various cranial nerves, including the seventh, ninth, and tenth. The geniculate-derived nerves provide innervation to the taste buds, ear lobes, and tonsils. The petrosal-derived nerves innervate the carotid sinus, body, and tongue. The nodose-derived vagus nerve provides innervation to several body organs, such as the heart, lungs, and gastrointestinal tract **[26].**

**C. The intermediate (trigeminal) placode:**

Found between the anterior and posterior placodes. It is responsible for developing the sensory neurons of the ophthalmic and maxilla-mandibular divisions of the trigeminal ganglion, which are involved in touch, temperature, and pain sensation of the face. While the distal neurons of the trigeminal ganglion originate from the trigeminal placode, the proximal neurons are derived from neural crest cells **[20].**

## 4. ORIGIN AND DEVELOPMENT OF NEUROGENIC PLACODES:

**a. The pre-placodal region (PPR): an exclusive domain holding progenitor cells for sensory placodes.**

Studies on chick **[27]** and various amphibians **[28, 29]** have used fate mapping to show that all placodes come from a small band of cells around the neural plate known as the pre-placodal field and share the expression of specific molecular markers **[28, 30].** All placodes originate from a shared region called the pre-placode ectoderm or pan-placodal primordium. This ectodermal region has a specific position and molecular identity along the dorsoventral and anteroposterior axes **[31, 32].**

After gastrulation, placode precursors are generated from the neural plate border region. These precursors populate the cranial ectoderm around the future fore-, mid-, and hindbrain but are not found in the trunk region **[6].** This specific area, referred to as pre-placodal region (PPR), comprises the sensory precursors that initially have the potential to develop into all types of placodes **[3] Fig. 2.**

**b. Specification of the PPR**

The process of differentiating pre-placodal cells from surrounding ectodermic territories involves tissue interactions facilitated by different signaling pathways, which results in the expression of specific transcriptional controllers [3]

**The 1st stage: Ectodermal separation:**

The undifferentiated ectodermic cells are divided into neuronal and non-neuronal ectodermic subdomains. BMP and Wnt transcription promote the non-neural ectoderm, while FGF transcription and inhibition of BMP and Wnt pathways promote the neuronal ectoderm **[27, 33] (Figure 1).**

**The 2nd stage: The establishment of a Neural Border (NB) zone**

The neural border (NB) zone encircles the neuronal plate and harbors cells with the potential to develop into placodes and neural crests. The neuronal (expressing Sox2) and non-neuronal (expressing Foxi1a/b) ectodermal fields are initially adjacent. However, a distinct area appears shortly afterward, lacking expression of both genes. This suggests the formation of a new intervening domain in the process **[34].**

**The 3rd stage: the neural border (NB) zone differentiation**

The NB zone differentiates into placodes and neural crest cells. There was a debate about whether they share common progenitors in the NB zone or not **[29].** Fate maps indicate massive intermingling within the NB zone suggesting a close spatial relationship and potential shared origins between neural crest cells and placodes during early development **[31].**

Signals from different tissues at different developmental stages induce the pre-placodal region (PPR) and neural crest, affecting cell fates and placode locations across the embryonic axis [3]. Factors promoting posterior development encourage neural crest formation while inhibiting PPR genes, restricting them to the cranial region. Additionally, Wnt competitors expressed in the head region enable the formation of PPR around the rostral end of the neuronal plate while preventing neural crest formation at this specific region **[3, 31].**

During gastrulation, placode progenitors are found to be dispersed. However, a continuous placode territory becomes clearly defined at the neurula stages. All placode precursors are concentrated within an ectodermic band encircling the neuronal plate, extending from the prosencephalon to the rhombencephalon **[28].** Placode cells commit to their final fate at a much later stage in development and give different tissues in response to specific signals **[20, 35],** so pre-placodal region (PPR) signifies a domain of multipotent progenitors **[6].**

**c. The vital role of The Six and Eya genes in placode development**

Six-Six genes (Six1-6) were found in mammals; however, just four Eya genes (Eya1-4) were discovered. Six proteins interact directly with Eya to attract co-activators that stimulate downstream target genes **[36]**. Although Six and Eya genes

are not the only transcription factors expressed in the pre-placodal region (PPR), they are among the first to be expressed throughout the PPR. **[31].**

Six1 has been reported to enhance the transcription of pre-placodal biomarkers while suppressing neural crest cells and neuronal plate development, implying a function in the specification of placode progenitors during the initial phases of development. However, in vertebrates, the amplification of Six1 and Eya2 does not result in aberrant placode development outside of the PPR, indicating the involvement of additional factors and complex regulatory mechanisms in placode development **[37].**The dysfunction of the Six and Eya genes plays a crucial role in developing sensory organs. Their involvement is specifically related to cell proliferation and neurogenesis. When Six1 or Eya1 is inactivated, defects in structures such as the inner ear, cranial ganglia, and olfactive epithelium are caused. Mutations in these genes are linked to the Branchial-Oto-Renal (BOR) syndrome, characterized by deafness, renal issues, and abnormalities in the branchial region **[38, 39].** The deficiency of Six1 and Eya1 function significantly affects the physiological development of nearly all placodes due to their widespread early expression and potential roles in the pre-placodal region (PPR).

**d. Interactive combined signaling pathways.**

**FGF pathway**

Fibroblast growth factors (FGFs) are believed to be the initial factor that confer pre-neuronal characteristics. They promptly induce the expression of genes like Sox3 and Geminin **[40]** and stimulate Dlx5 and Msx1 expression around **[30].** Eventually, these genes are co-expressed at the NB, generating placode and neural crest **[6].** FGF signaling is necessary for the expression of border genes and the formation of the neuronal border derivatives; it alone is not enough to create these derivatives outside the border territory. Furthermore, FGF8 triggers the expression of the pre-placodal region (PPR) biomarker Eya2, indicating its potential dual role in identifying placode precursors **[30].**

**BMP pathway**

Bmp signaling is linked to early ectodermal patterning **[41].** Bmp activity gradients in the ectoderm determine distinct cell fates: elevated levels promote the epidermis, moderate amounts induce placodes, intermediate amounts specify neural crest, and a total lack of Bmp activity is required for neural plate development **[42].**

**Wnt pathway**

Inhibiting BMP signaling increases the transcription of pre-placodal markers, and FGF8 encourages Eya2 expression. Nevertheless, the combination of Fgfs and Bmp competitors cannot independently induce pre-placodal properties in ectoderm beyond the natural placode area. This indicates that additional signals are necessary for this process **[30].**

Blocking the canonical Wnt pathway expands the neural plate **[43].** Conversely, Wnt transcription is critical for the development of neural crest **[44].** Modulating Wnt signaling has a significant impact on pre-placodal cells: Wnt antagonists expand the pre-placodal region (PPR), whereas activating the Wnt signals inhibits the genes specific to the PPR **[30]**

In summary, the development of placode precursors involves the integration of various signals, leading to the simultaneous expression of specific genes like Six1,-4, and Eya1,-2. Initially, FGFs induce a pre-neural state shared by the neural plate, neural crest, and placode precursors, maintaining their multipotency. BMP signaling promotes non-neural traits and restricts the neural plate's size. BMP, along with FGFs, sustains and enhances border gene expression. Local changes in Wnt signaling determine whether border cells become neural crest or placode precursors. Notably, the signals guiding placode precursor development resemble those for neural identity, suggesting common early steps in their induction **[6].**

The precise timing of Wnt and BMP expression is crucial in determining the fate of ectodermal tissues, including neuronal plate, epidermis, placodes, and neural crest. Continuous signaling leads to the ectodermal cells adopting an epidermal fate. However, if BMP signaling is blocked by BMP antagonists (such as FGFs), the ectodermal cells adopt the neural state. The cells form placodes when Wnts generate BMPs and switch off Wnt signals. On the other hand, if BMPs are induced by Wnt and Wnt continues signaling, the cells can develop into neural crest tissues **[45, 46] (Figure 2).**

## 5. SPECIFICATION AND SUBDIVISION OF THE PRE-PLACODAL REGION

During the neurula stages, the PPR and neuronal plate are segregated into distinct areas along the rostro-caudal axis. There is a rostral Otx2-expressing area and a caudal Gbx2-expressing area. These two factors reciprocally inhibit each other, reinforcing the borders separating potential placodal territories and defining each placodal area **[47].** In this process, Otx2

controls the initiation of the anterior group placodes, olfactory, lens, intermediate placodes, and trigeminal placodes, whereas Gbx2 controls the induction of the posterior placodes and otic placode **[3].**

**e. The specification of the anterior placodes**

Four key signaling pathways control the developmental process of the anterior placodes: FGF, BMP, SHH, and WNTs. Pax6 is the first marker for the anterior placodes, which is thought to be triggered by SIX1 inside the anterior area. **[37].** Regardless of their eventual fate, all placodes exhibit shared characters and are specified as lens cells expressing Pax6. However, other signals inducing placode development must suppress this initial tendency to express Pax6. Initially, there is co-expression of Pax6 and Dlx5 in the potential eye-lens and olfactive placodes. As these placodal fates are differentiated, brief exposure to BMP4 results in temporary downregulation of Pax6 by FGF8 in the prospective olfactory placode. Conversely, with prolonged BMP4 exposure, downregulation of Dlx5 expression in the future lens is present **[35].**

Signaling through the Sonic Hedgehog (Shh) pathway is crucial in multiple stages of adenohypophysis development. This includes the initial commitment to specific cell lineages and subsequent differentiation. Additionally, Shh signaling suppresses the formation of lens and olfactory placodes during these developmental processes **[48].**

**f. The specification of the posterior placodes**

FGF signaling is considered the primary regulator of the caudal placodal area, which is known as the otic-epibranchial placode domain (OEPD), and differentiates into otic and epibranchial placodes, it upregulates the expression of Pax2 and Pax8 in the otic- OEPD **[24].** FGF signaling and WNT inhibition promote the development of the epibranchial placode fate. On the other hand, FGF signaling and WNT activation induce the otic placode **[49].** The absence of either dlx3b/4b or foxi1 leads to the formation of smaller otic vesicles. However, when both dlx3b and foxi1 are lost simultaneously, this leads to defective otic placode induction and complete absence of the otic vesicle **[50, 51].**

**g. The specification of the intermediate placodes**

The trigeminal placode is split into ophthalmic and maxillomandibular divisions and develops right close to the midbrain. Pax3 is the first trigeminal placode marker activated by the combined signaling of WNT and FGF. In addition, PDGF and Notch signaling are involved in the production of trigeminal placodes. **[52].** During trigeminal placode development, these signaling molecules also influence the final stages of neural differentiation. Pax6 repression is caused by the stimulation of Pax3 in the middle pre-placodal area, which aids in the appropriate localization and division between the anterior and middle placode regions **[53].**

## 6. CONCLUSION

Ectodermal placodes are specialized areas of cells in the head that give rise to sensory and non-sensory structures like sense organs, hair, teeth, and skin coverings. These placodes develop from the pre-placodal region, which is induced by FGF signaling and inhibited by Wnt and Bmp pathways. The pre-placodal region is then divided into individual placodes, with local signals from the neural tube and the underlying mesoderm or endoderm regulating the process.

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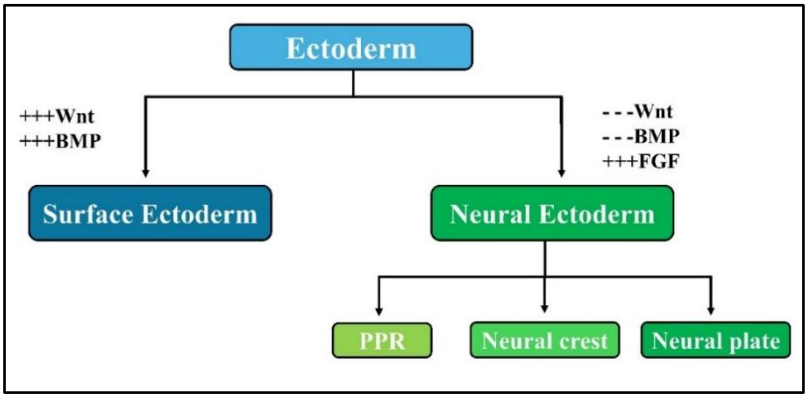


**Fig. 1. Schematic representation of the ectodermal differentiation, ++ increased expression, -- inhibit expression**

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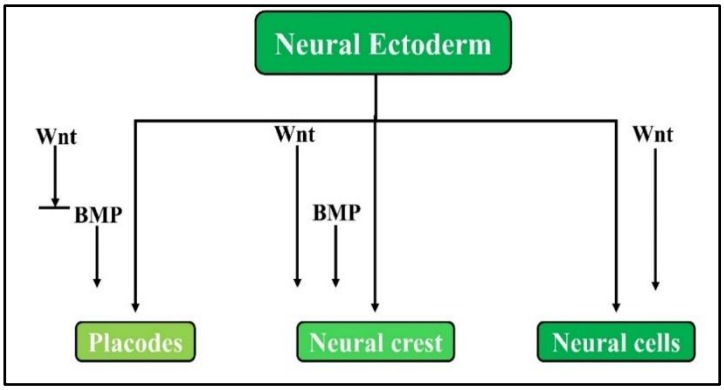


**Fig. 2. Schematic representation of the role of Wnt and BMP in the differentiation of neural ectoderm.**

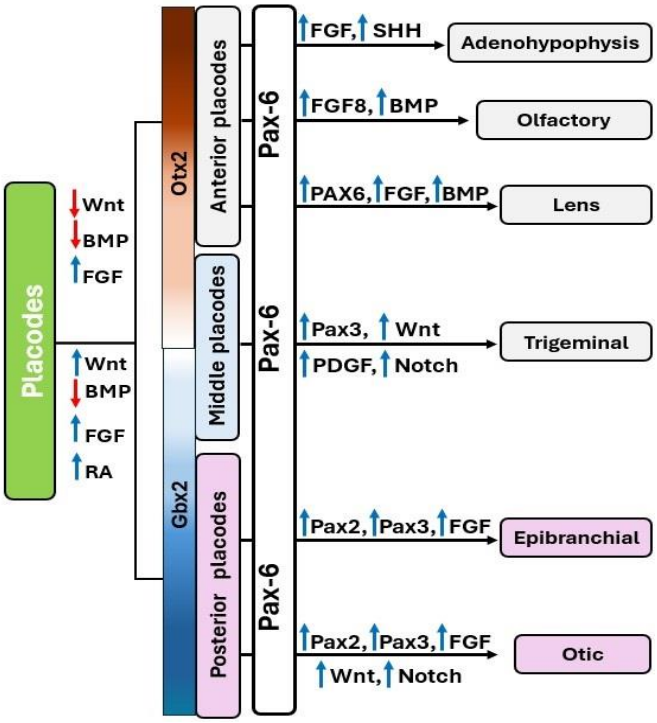


**Fig. 3. Schematic representation of division and differentiation of the pre-placodal region.**

## REFERENCES

[1] Phuong Le, A., J. Kim, and K.R. Koehler, *The mechanical forces that shape our senses.* Development, 2022. **149**(7): p. dev197947.

[2] Barresi, M.J.F. and S.F. Gilbert, *Developmental biology*. 12th edition ed. 2019: Sinauer Associates is an imprint of Oxford University Press; .

[3] Saint-Jeannet, J.-P. and S.A. Moody, *Establishing the pre-placodal region and breaking it into placodes with distinct identities.* Developmental biology, 2014. **389**(1): p. 13-27.

[4] Moody, S.A. and A.S. LaMantia, *Transcriptional regulation of cranial sensory placode development.* Curr Top Dev Biol, 2015. **111**: p. 301-50.

[5] Pispa, J. and I. Thesleff, *Mechanisms of ectodermal organogenesis.* Dev Biol, 2003. **262**(2): p. 195-205.

[6] Streit, A., *Specification of sensory placode progenitors: signals and transcription factor networks.* Int J Dev Biol, 2018. **62**(1-2-3): p. 195-205.

[7] Froriep, A., *Ueber Anlagen von Sinnesorganen am Facialis, Glossopharyngeus und Vagus, über die genetische Stellung des Vagus zum Hypoglossus, und über die Herkunft der Zungenmuskulatur: Beitrag zur Entwickelungsgeschichte des Säugethierkopfes*. 1885: éditeur inconnu.

[8] Beard, J., *On the Branchial Sense-Organs of the Ichthyopsida.* Quart. Jour. Micr. Sci., 1886. **25**.

[9] Strong, O.S., *The cranial nerves of amphibia*. Vol. 1. 1895: Ginn.

[10] von Kupffer, C., *Studien zur vergleichenden Entwicklungsgeschichte des Kopfes der Kranioten*. Vol. 1. 1893: JF Lehmann.

[11] von Kupffer, C., *Studien zur verleichenden entwicklungsgeschichte des kopfes der kranioten: hft. Die entwicklung der kopfnervon von Ammocoetes planeri*. 1895: JF Lehmann.

[12] Landacre, F. and M.F. McLellan, *The cerebral ganglia of the embryo of Rana pipiens.* The Journal of Comparative Neurology, 1912. **22**(5): p. 461-486.

[13] Landacre, F., *The cerebral ganglia and early nerves of Squalus acanthias.* The Journal of Comparative Neurology, 1916. **27**(1): p. 19-67.

[14] Batten, E.H., *The activity of the trigeminal placode in the sheep embryo.* J Anat, 1957. **91**(2): p. 174-87.

[15] Stark, M.R., et al., *Neural tube-ectoderm interactions are required for trigeminal placode formation.* Development, 1997. **124**(21): p. 4287-95.

[16] Couly, G.r. and N.M.L. Douarin, *The fate map of the cephalic neural primordium at the presomitic to the 3-somite stage in the avian embryo.* Developmental biology, 1988. **103**(Supplement): p. 101-113.

[17] Couly, G.F. and N.M. Le Douarin, *Mapping of the early neural primordium in quail-chick chimeras. II. The prosencephalic neural plate and neural folds: implications for the genesis of cephalic human congenital abnormalities.* Dev Biol, 1987. **120**(1): p. 198-214.

[18] Baker, C.V., et al., *Competence, specification and induction of Pax-3 in the trigeminal placode.* Development, 1999. **126**(1): p. 147-56.

[19] Begbie, J., et al., *Induction of the epibranchial placodes.* Development, 1999. **126**(5): p. 895-902.

[20] Baker, C.V. and M. Bronner-Fraser, *Vertebrate cranial placodes I. Embryonic induction.* Dev Biol, 2001. **232**(1): p. 1-61.

[21] Rizzoti, K., *Genetic regulation of murine pituitary development.* J Mol Endocrinol, 2015. **54**(2): p. R55-73.

[22] Cvekl, A. and M.K. Duncan, *Genetic and epigenetic mechanisms of gene regulation during lens development.* Prog Retin Eye Res, 2007. **26**(6): p. 555-97.

[23] Wray, S., *Development of gonadotropin-releasing hormone-1 neurons.* Front Neuroendocrinol, 2002. **23**(3): p. 292-316.

[24] Ladher, R.K., P. O'Neill, and J. Begbie, *From shared lineage to distinct functions: the development of the inner ear and epibranchial placodes.* Development, 2010. **137**(11): p. 1777-85.

[25] Thomas, E.D., et al., *There and back again: development and regeneration of the zebrafish lateral line system.* Wiley Interdisciplinary Reviews: Developmental Biology, 2015. **4**(1): p. 1-16.

[26] Schlosser, G. and R.G. Northcutt, *Development of neurogenic placodes in Xenopus laevis.* J Comp Neurol, 2000. **418**(2): p. 121-46.

[27] Streit, A., *Extensive cell movements accompany formation of the otic placode.* Dev Biol, 2002. **249**(2): p. 237-54.

[28] Streit, A., *Early development of the cranial sensory nervous system: from a common field to individual placodes.* Dev Biol, 2004. **276**(1): p. 1-15.

[29] Pieper, M., et al., *Origin and segregation of cranial placodes in Xenopus laevis.* Dev Biol, 2011. **360**(2): p. 257-75.

[30] Litsiou, A., S. Hanson, and A. Streit, *A balance of FGF, BMP and WNT signalling positions the future placode territory in the head.* Development, 2005. **132**(18): p. 4051-62.

[31] Grocott, T., M. Tambalo, and A. Streit, *The peripheral sensory nervous system in the vertebrate head: a gene regulatory perspective.* Dev Biol, 2012. **370**(1): p. 3-23.

[32] Groves, A.K. and C. LaBonne, *Setting appropriate boundaries: fate, patterning and competence at the neural plate border.* Developmental biology, 2014. **389**(1): p. 2-12.

[33] Rogers, C.D., S.A. Moody, and E.S. Casey, *Neural induction and factors that stabilize a neural fate.* Birth Defects Research Part C: Embryo Today: Reviews, 2009. **87**(3): p. 249-262.

[34] Matsuo-Takasaki, M., M. Matsumura, and Y. Sasai, *An essential role of Xenopus Foxi1a for ventral specification of the cephalic ectoderm during gastrulation.* Development, 2005. **132**(17): p. 3885-94.

[35] Bhattacharyya, S. and M. Bronner-Fraser, *Competence, specification and commitment to an olfactory placode fate.* Development, 2008. **135**(24): p. 4165-77.

[36] Hu, S., A. Mamedova, and R.S. Hegde, *DNA-binding and regulation mechanisms of the SIX family of retinal determination proteins.* Biochemistry, 2008. **47**(11): p. 3586-94.

[37] Christophorou, N.A., et al., *Activation of Six1 target genes is required for sensory placode formation.* Developmental biology, 2009. **336**(2): p. 327-336.

[38] Whitfield, T.T., *Lateral line: precocious phenotypes and planar polarity.* Curr Biol, 2005. **15**(2): p. R67-70.

[39] Zou, D., et al., *Eya1 regulates the growth of otic epithelium and interacts with Pax2 during the development of all sensory areas in the inner ear.* Developmental biology, 2006. **298**(2): p. 430-441.

[40] Papanayotou, C., et al., *A mechanism regulating the onset of Sox2 expression in the embryonic neural plate.* PLoS Biol, 2008. **6**(1): p. e2.

[41] Stern, C.D., *Neural induction: old problem, new findings, yet more questions.* Development, 2005. **132**(9): p. 2007-21.

[42] Vonica, A. and A.H. Brivanlou. *An obligatory caravanserai stop on the silk road to neural induction: inhibition of BMP/GDF signaling*. in *Seminars in cell & developmental biology*. 2006. Elsevier.

[43] Heeg-Truesdell, E. and C. LaBonne, *Neural induction in Xenopus requires inhibition of Wnt-β-catenin signaling.* Developmental biology, 2006. **298**(1): p. 71-86.

[44] Knecht, A.K. and M. Bronner-Fraser, *Induction of the neural crest: a multigene process.* Nat Rev Genet, 2002. **3**(6): p. 453-61.

[45] Piacentino, M.L. and M.E. Bronner, *Intracellular attenuation of BMP signaling via CKIP-1/Smurf1 is essential during neural crest induction.* PLoS biology, 2018. **16**(6): p. e2004425.

[46] Patthey, C. and L. Gunhaga, *Specification and regionalisation of the neural plate border.* Eur J Neurosci, 2011. **34**(10): p. 1516-28.

[47] Steventon, B., R. Mayor, and A. Streit, *Mutual repression between Gbx2 and Otx2 in sensory placodes reveals a general mechanism for ectodermal patterning.* Developmental biology, 2012. **367**(1): p. 55-65.

[48] Kelberman, D., et al., *Genetic regulation of pituitary gland development in human and mouse.* Endocr Rev, 2009. **30**(7): p. 790-829.

[49] Freter, S., et al., *Progressive restriction of otic fate: the role of FGF and Wnt in resolving inner ear potential.* Development, 2008. **135**(20): p. 3415-24.

[50] Solomon, K.S., S.J. Kwak, and A. Fritz, *Genetic interactions underlying otic placode induction and formation.* Dev Dyn, 2004. **230**(3): p. 419-33.

[51] Birol, O., et al., *The mouse Foxi3 transcription factor is necessary for the development of posterior placodes.* Developmental biology, 2016. **409**(1): p. 139-151.

[52] Lassiter, R.N., et al., *Sensory neuron differentiation is regulated by notch signaling in the trigeminal placode.* Developmental biology, 2010. **344**(2): p. 836-848.

[53] Voelkel, J.E., et al., *FGF and Notch signaling in sensory neuron formation: a multifactorial approach to understanding signaling pathway hierarchy.* Mech Dev, 2014. **134**: p. 55-66.