



## Recent advances in the regulation mechanism of *SOX10*

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### ABSTRACT

Neural crest (NC) is the primitive neural structure in embryonic stage, which develops from ectodermal neural plate cells and epithelial cells. When the neural fold forms into neural tube, neural crest also forms a cord like structure above the neural tube and below the ectoderm. Neural crest cells (NCC) have strong migration and proliferation abilities. A number of tissue cells differentiate from neural crest cells, such as melanocytes, central and peripheral neurons, glial cells, craniofacial cells, osteoblasts, chondrocytes and smooth muscle cells. The migration and differentiation of neural crest cells are regulated by a gene network where a variety of genes, transcriptional factors, signal pathways and growth factors are involved.

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*Sox10* (Sry-box 10) is a key gene in the regulation (SOMMER, 2011). *Sox10* gene, as a member of Sox E family, plays an important role in regulating the formation and development of tissues

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and organs which derive from neural crest in embryonic stage (HERBARTH et al., 1998). During the above process, *Sox10* gene also maintains pluripotency, and its mutation leads to neural crest diseases, such as Waardenburg syndrome that is a common congenital deafness syndrome. Therefore, exploring signal pathways and gene regulation network in which *Sox10* gene participates in will provide a better understanding of the pathogenesis of neural crest disorders induced by *Sox10* gene mutation.

This review elaborates the recent research advance on regulation mechanism of *Sox10* gene in the development of cells originated from neural crest, such as glial cells and melanocytes. It will provide a deep understanding of *Sox10* gene regulation network and a theoretical basis for researching the pathogenesis of neural crest related disease caused by *Sox10* gene mutation. Last, it summarizes that molecular mechanisms of inner ear development derived from studies of *Sox10* gene mutation, which will facilitate further research on how *Sox10* affect the function of inner ear.

### 1. An overview of *Sox10* gene and protein

#### 1.1. *Sox10* gene

*Sox* (Sry-related HMG box) gene, one of a super gene family, of which protein-coding contains highly active component structural motif HMG (high mobility group), is closely related to sex determinant genes (Sex determining region Y, Sry). This motif is highly conserved in eukaryotes, which combines with other transcriptional factors and binding to target DNA in a sequence-specific manner (Gubbay et al., 1990; WEGNER, 1999; BOWLES et al., 2000). Comparing with HMG motifs, Wright (WRIGHT et al., 1993) and Bowles (BOWLES et al., 2000) et al. divided *Sox* gene family into 8 subfamilies-*Sox* A-H. *Sox10* (Sry-box 10) gene, a member of *Sox* E family, is located on chromosome 22q13.1, which contains 5 exons as well as exon 03, 04 and 05 encode protein. *Sox10* encode 466 amino acids and a protein weighing 51kD, and its cDNA is 1.4 kb at full length.

#### 1.2. *Sox10* protein

The N-terminal of *Sox10* protein contains a dimerization domain (DD), which is vital to the protein dimer to bind with target gene. This domain comprises 40 amino acids and is highly conserved in the *Sox* E family (PEIRANO, 2000). Next to it is a 79-amino acids HMG domain, where includes an intron and a 73-amino acids K2 domain (SCHREINER et al., 2007). The C-terminal contains a transcription activation threshold with 66 amino acids, which is rich in serine, proline and glutamine sequences (PUSCH et al., 1998). It regulates the function of *Sox10* protein by binding and interacting with specific molecules. As other members of the family, *Sox10* protein specifically recognizes and binds to the target gene sequence 5'-(A/T)(A/T)CAA(A/T)G-3' with HMG box (HARLEY et al., 1994). *Sox10* protein functions as two different DNA response elements. It is unique that the conformation of the DNA is modified by binding monomer or dimer to target genes. Compared to monomer, dimer increases DNA binding affinity and affects DNA bending. Monomer and dimer bind to different DNA promoters of target genes forming optimal conformation (PEIRANO, 2000; SCHLIERF, 2002). *Sox10* is an active nucleocytoplasmic shuttle protein, and it contains two nuclear localization signals making *Sox10* shuttle between nucleus and cytoplasm, which are critical for *Sox10* mediated transcriptional activation. Besides, *Sox10* protein can also bind to the upstream cis acting elements of the target gene directly or indirectly to further regulate the expression of the target gene (SOMMER, 2011; Liu et al., 2014). In turn, post-translational modifications such as methylene, phosphorylation and acetylation also

affect the function of *Sox10* protein.

#### 1.3. Expression and regulation of *Sox10* gene and protein

*Sox10* gene plays a key role in the maintenance, migration and differentiation of neural crest progenitor cells. *Sox10* is first expressed in the dorsal neural tube, and then it is expressed in its derivatives as cell differentiation, which contributes to the formation of the peripheral nervous system (HERBARTH et al., 1998; AOKI et al., 2003). In the group of adult mice and humans, it is expressed at a high level in brain, inner ear, heart and intestinal tract and at a low level in prostate, testis, bladder, pancreas and stomach (Owen et al., 2016). In peripheral nervous system, most neurons and all glial cells originate from the neural crest. *Sox10* is no longer expressed in mature neuronal cells but continues to be expressed in mature glial cells (KUHLEBRODT et al., 1998). In central nervous system, mainly in oligodendrocytes, *Sox10* is crucial to their differentiation, maturation and myelination (LI et al., 2007). As to melanocytes, *Sox10* gene significantly and persistently affect its specialization, maturation and maintenance (AOKI et al., 2003). In the early stage of inner ear development, *Sox10* is widely expressed. After hair cells matured, *Sox10* expression is gradually limited to support cells (WATANABE et al., 2000; LOCHER et al., 2013). It is the gene regulation network, centered on *Sox10* gene that plays an important role during the migration of neural crest cells (Owen et al., 2016) (Fig. 1a). Its expression in neural crest is regulated by signal transduction pathways, such as Wnts, BMPs and FGFs (AOKI et al., 2003; KIM et al., 2003; HONORÉ et al., 2003; WERNER et al., 2007).

*Sox10* protein is a key transcription factor for the migration and differentiation of neural crest derived cells, and it function alone or in cooperation with other transcription factors (Liu et al., 2014). Yeast two-hybrid analysis shows that more than a dozen transcription factors, such as *Dlx5*, *Alx4*, *Hoxa3*, *BRN-1* and *Pax3*, regulate the transcriptional activity of *Sox10* by binding N-terminal of *Sox10* HMG domain with their DNA binding domain (WISSMULLER, 2006).

### 2. Regulation of *Sox10* protein in the development of glial cells

*Sox10* protein specifically enhances transcription in glial cells, and it is necessary for the terminal differentiation and maintenance of central nervous glial cells and oligodendrocytes and indispensable in the whole process of migration, survival and differentiation of peripheral glial Schwann cells (WEIDER and WEGNER, 2017).

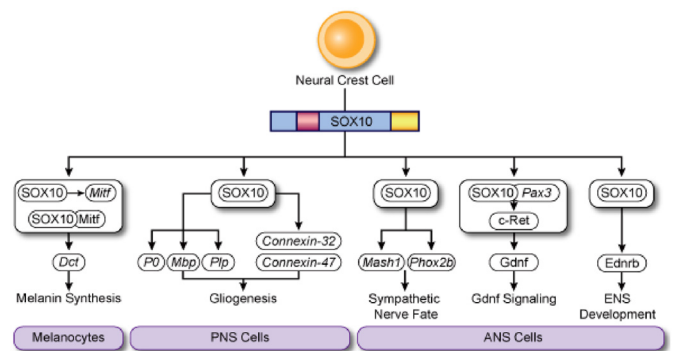


Fig. 1.1. *Sox10* expression and regulation network during neural crest cell migration (Owen et al., 2016).

### 2.1. Effect of Sox10 protein on the development of schwann cells

Sox10 protein is co-expressed with POU domain proteins *tst-1/OCT6/SCIP*, *Pax3* and *Egr2/Krox-20* at some stages of Schwann cell development. They synergistically bind with the target gene at the N-terminal region (KUHLEBRODT et al., 1998). Protein zero (P0) gene encoding myelin protein P0 is the direct transcription target of *Sox10*. *Sox10* protein regulates its expression by directly acting on the B, C and F sites of MPZ gene promoter. The expression of heterozygous P0 gene in *Sox10* mutant DOM mice decreases, and it is hardly detected in homozygous (PEIRANO et al., 2000). Connexin 32 (Cx32) plays a role in the molecular transport of Schwann cells, which is encoded by *GJB1* gene. In the development of Schwann cells, *Sox10* activates the promoter of *GJB1* gene by acting on S1 and S2 sites synergistically with *Pax3*, *pou3f1* and *Egr2* (BONDURAND, 2001). *Sox10* directly activates *Egr2* or cooperates with *Egr2* gene to activate downstream target genes *MBP*, *MAG*, *DHH*, etc. (SRINIVASAN et al., 2012; JANG et al., 2006). *Sox10* protein binds to the enhancer site MSE of *Krox20* through the K2 domain of HMG and the POU domain of *OCT6*, to activate the expression of *Krox20* (REIPRICH et al., 2010). The encoded *Krox20* protein, in turn, activates the expression of target genes together with *Sox10*. This *Sox10* transcription dependent linkage pattern plays an important role in Schwann cell development. *ErbB3* is a key gene in the development and differentiation of neural crest derived tissue cells. The encoded protein belongs to a tyrosine kinase receptor of the epithelial growth factor (EGF) receptor family. *ErbB3* activates downstream pathways *PI3K*, *MAPK*, *PKC*, *JAK stat* and *PLCG* (BRITSCH, 2007). *Sox10* regulates expression of *ErbB3* by direct combination with enhancer *ERBB3-Mcs6* (PRASAD et al., 2011).

At the non-myelinating stage of Schwann cell development, *Sox10* protein activates the expression of genes *SOX5*, *Sox6*, *Notch1*, *HMGA2*, *Hes1*, *MYCN*, *ID4* and *Id2* that inhibit myelination, preventing premature differentiation of glial cells (GOPINATH et al., 2016). During the development of Schwann cells, *Sox10-egr2/Krox-20* pathway and *Sox10-ERBB3* pathway regulate in a complex network.

### 2.2. Effect of Sox10 protein on the development of oligodendrocytes

*Sox10* and *Sox9* proteins bind to *PDGF $\alpha$*  receptor of oligodendrocyte precursors, promoting their survival and migration abilities, and keep them in an undifferentiated state. *Sox10*, *Sox5* and *Sox6* synergistically activate the *PDGF $\alpha$*  receptor promoter and keep oligodendrocytes in an immature state (FINZSCH et al., 2008; BAROTI et al., 2016). *MYRF* (myelin regulatory factor) is an important transcriptional regulator to the formation of myelin in the central nervous system. *Sox10* induces the expression of *MYRF* in oligodendrocytes by combining HMG and DD domains with the enhancer *ECR9* at the C-terminal of *MYRF*, and then cooperates with *MYRF* to activate the expression of myelin gene. This regulatory network is very important to the differentiation and maturation of oligodendrocytes (HORNIG et al., 2013), which is functionally equivalent to the regulation of *Krox20* and *Egr2* in Schwann cells. *Olig1* and *Olig2* are members of the bHLH transcription factor family. *Sox10* binds to the bHLH domains of *Olig1* and *Olig2* with its HMG domain (LI et al., 2007; KÜSPERT et al., 2011), and they jointly activate the expression of *Mbp* and *Plp* genes and promote the terminal differentiation of oligodendrocytes. In oligodendrocytes, *Sox10* upregulates *miR 335* and *miR 338*. These two microRNAs in turn recognize the 3'UTR of *Sox9* mRNA, reducing *Sox9* expression in oligodendrocytes. This process maintains the balance of the *Sox10* and *Sox9*, contributing to the terminal differentiation of oligodendrocytes (REIPRICH et al., 2017). Activated T-cell nuclear factor 2 (NFAT2) is ubiquitous in

mammalian cells. It participates in multiple signal pathways and is closely related to growth and complex cell interactions. *Sox10* affects the differentiation and myelination of oligodendrocyte by participating in the calcineurin/NFAT signaling pathway (WEIDER et al., 2018).

### 3. Effect of Sox10 protein on the development of melanocytes and melanoma cells

*Sox10* protein is a key transcription factor to the establishment and maintenance of melanocyte lineage, and that is related to the occurrence, proliferation and invasion of melanoma. Literature (BONDURAND, 2000; POTTERF et al., 2000; ELWORTHY, 2003; LEE et al., 2000; HARRIS et al., 2010) has suggested that *MITF* is the target gene of *Sox10* protein, and *Sox10* protein bind to M promoter of *MITF* to activate transcription directly or cooperate with *PAX3*. *MITF* protein is a nuclear transcription factor with basic domain helix-loop-helix leucine zipper (bHLH-Zip) domain. There are four common subtypes, *MITF-A*, *MITF-C*, *MITF-H* and *MITF-M*, among which *MITF-M* is expressed in melanocytes and melanoma cells. *MITF* protein is the main regulator of development and migration of melanocytes derived from neural crest, and its mutation causes abnormalities. Dopachrome tautomerase (*DCT*), tyrosinase (*TYR*) and *TYR*-related protein 1 (*TYRP1*) are key enzymes to melanin synthesis, which is regulated by *MITF* and *Sox10*. Transcriptional activation experiments in vitro determines that *Sox10* and *MITF* synergistically activate *DCT* (JIAO et al., 2004; LUDWIG et al., 2004). Besides, *Sox10* bind to the core enhancers in regulatory elements (*DRE*) of *TYR*, and *MITF* indirectly regulates the transcriptional activation of tyrosinase gene by combining with the E-box sequence of promoter (MURISIER et al., 2007). In conclusion, *Sox10-MITF* pathway is important in regulating the development of melanocytes. *KIT* is a tyrosine kinase receptor protein, which is essential for the survival, growth, differentiation and migration of melanocytes. Fufa et al. (FUFA et al., 2015) discover that in melanocytes *Sox10* protein inhibits the expression of *KIT* gene by binding to its homeopathic response element. The results also show that lack of *Sox10* haploid upregulate and downregulate the expression of downstream genes at the same time. More importantly, they reveal a new aspect of *Sox10* mediated gene regulation, pluripotency (self-renewal) and EMT (epithelial mesenchymal transition), which is related to early development and metastasis of cancer. Consumption of *Sox10* leads to cell cycle arrest, aging and inhibition of melanoma. The key point to the occurrence of melanoma is the development of multipotent stem cells with characteristics of melanocytes. Then *nestin*, *cd-271* and *cd-133*, are expressed. These factors are directly or indirectly regulated by *Sox10* gene to inhibit apoptosis and promote the occurrence of melanoma (TUDREJ and EDYTA, 2017). Besides, *Sox10* gene also plays an essential role in regulating the invasion of melanoma.

Peripheral myelin protein 2 (*PMP2*) is the target gene directly regulated by *Sox10* in melanoma cells, while *Egr2* participates in the regulation as a cofactor and promotes the invasion of melanoma. There are three conserved *Sox10* gene binding sites (*P1*, *P2* and *P3*) in the *PMP2* promoter region (GRAF et al., 2019). Melanoma inhibitory activity (*MIA*) is vital to the migration and invasion of melanoma cells. *Sox10* directly regulates *MIA*, as well as indirectly regulate *MIA* by cooperating with the binding factor near promoter region (GRAF et al., 2014). Inhibition of *Sox10* activity in melanoma cells leads to apoptosis and necrosis, implying that *Sox10* protein is vital for the survival and proliferation of melanoma cells.

### 4. Effect of Sox10 protein on the development of inner ear

The inner ear composes of cochlea and vestibule, and its

structure is complex and fine. The cochlear system senses sound and transmit a series of bioelectrical signals to the auditory center after preliminary analysis. The vestibular system senses and transmits balance signals. Therefore, the inner ear is important for auditory generation and balance maintenance. The development of mature inner ear from ear substrate is extremely complex in mammals. The membranous labyrinth cells of inner ear originate from the ear plate of the ectoderm, they invaginate and form the ear sac. After differentiation, they finally form the terminal organ of hearing and balance. This process is developing in an orderly manner and is accurately regulated by a variety of genes. Embryonic development is a chain reaction; different genes are activated successively, with time and space specificity. In the early stage of ear basal plate development, cranial neural crest cells differentiate into forebrain, midbrain and hindbrain. The cranial neural crest cells of the hindbrain continue to differentiate into the rhomboid proto ganglion, the ectoderm outsidess continue to form the ear substrate (Liu et al., 2014), then neural crest cells migrate to the inner ear to form the intermediate cells of the stria vascularis and the glial cells of the vestibular cochlear nerve. *Sox10* gene plays an important regulatory role in the maintenance, migration and differentiation of neural crest cells, and it is widely expressed in neural crest derived and non-neural crest derived cells in the early development of inner ear (Liu et al., 2014; WATANABE et al., 2000; BREUSKIN et al., 2009; DUTTON et al., 2009). *Sox10* gene mutation causes Waardenburg syndrome in human. Clinically, the probability of inner ear malformation in Waardenburg cases with *Sox10* gene mutation is significantly higher than that with other gene mutations, and the proportion of vestibular dysplasia is high, which includes vestibular cistern enlargement and absence of semicircular canal (PINGAULT et al., 2015; XU et al., 2016). *Sox10* gene mutation animal model also confirms that its mutation is associated with abnormal development of inner ear (HERBARTH et al., 1998; BREUSKIN et al., 2009; DUTTON et al., 2009; BRITSCH, 2001; HAI et al., 2017; HAO et al., 2018). However, the regulatory effect of *Sox10* gene on the embryonic development of inner ear is not fully understood.

#### 4.1. Effect of *Sox10* protein on the development of vestibule and cochlear in the inner ear

Inner ear malformations (IEM) are caused by heredity, drug, virus infection and other factors, which affect the normal development of the inner ear. Inner ear malformation occurs in any part of the membranous labyrinth and bone labyrinth, accounting for 80% and 20% respectively. In membranous labyrinth, hair cells are often involved and imaging examination often cannot detect, while in bone labyrinth, imaging examination can be used to confirm the malformation (SENNAROGLU and BAJIN, 2017). Vestibular hair cells can sense the change of head position and maintain the balance of the body. In the development of vestibular system from dorsal ear sac, many genes are involved. *Otx1*, *Otx2*, *PAX2*, *Fgf8*, *BMP4* and other genes are all important in the development (BURTON et al., 2004; MORSLI et al., 1998; CANTOS et al., 1170; MERLO et al., 2002; SÁNCHEZ-CALDERÓN et al., 2004; CHANG et al., 2008; DOMÍNGUEZ-FRUTOS et al., 2009). Kirsten Dutton et al. (DUTTON et al., 2009) found that in the early development of zebrafish with *Sox10* gene mutation, due to the absence of *Sox10* protein, the expression of downstream genes is affected, such as *Fgf8* and *BMP4*, which are essential for the normal development of the vestibule of the inner ear. Therefore, *Sox10* gene mutation in zebrafish causes abnormal development of vestibule, such as semicircular canals, cystic plaques and endolymphatic vessels, indicating that *Sox10* gene plays a key role in the normal gene expression in the early stage of vestibular system development. *Sox10* gene mutation has a

more serious impact on the development of the inner ear of *Xenopus laevis*, which leads to abnormal development of neural crest and loss of ear sac (AOKI et al., 2003; HONORÉ et al., 2003; LANG, 2003). In the established *Sox10* gene mutant mouse model and miniature pig model, no obvious abnormalities were found in the general morphology of vestibule during embryonic development (BREUSKIN et al., 2009; HAI et al., 2017; HAO et al., 2018), but the differentiation and development of vestibular sensory epithelium has not further studied. Wnt signaling pathway has been proved significant for the development of vestibular system, especially *Wnt1* and *Wnt 3a* (RICCOMAGNO, 2005; BROWN et al., 2015). Wnt pathway signaling molecules from the dorsal hindbrain region regulate the expression of genes in the dorsal region of the ear sac, such as *Dlx5/6*, *Gbx2* and *hmx2/3*. These genes play an important regulatory role in the development of the vestibular system (ROBLEDO and LUJKIN, 2006; LIN, 2005; WANG et al., 2004). It is reported that if *Wnt1* and *Wnt 3a* genes were knocked out at the same time, utricle and saccule were unable to develop. The pathological mechanism may be the reduction of the expression of *Dlx5* and *Gbx2* genes which affects vestibular development (RICCOMAGNO, 2005). Qing Hao et al. (HAO et al., 2018) studied the molecular biological mechanism of inner ear malformation caused by *Sox10*<sup>p.r109w</sup> mutant in miniature pig. High throughput transcriptome sequencing and bioinformatics analysis shows that the possible target gene of *Sox10* gene regulating inner ear development is *Wnt1*. In conclusion, Wnt signaling pathway plays a key role in the development of vestibular system.

*Sox10* gene mutation could also cause Waardenburg sensorineural hearing loss. In the early stage, it is considered that *Sox10* gene affects the expression of melanin related genes such as *MITF* and *DCT*, resulting in the deletion of stria vascularis intermediate cells, thus it affects the disturbance of endolymphatic circulation and causes the hypoplasia of Corti organ (TACHIBANA, 1999; TORIELLO, 2011). However, pathological mechanism of abnormal development of inner ear caused by *Sox10* gene still needs to be explored. *Sox10* gene is widely expressed in the early stage of inner ear development, but it is no longer expressed in differentiated and mature hair cells. So far, for different *Sox10* gene mutation animal models, homozygous mutants have embryonic lethality, while heterozygotes have different phenotypes. The research of cochlear malformation caused by *Sox10* gene mutation is a hot spot. In *Xenopus laevis*, the ear sac of is missing; in the homozygous mouse model, the cochlear canal is significantly shortened; in the heterozygous mouse model, the cochlear canal is extended and hair cells and Sertoli cells of Corti's organ are missing. In the miniature pig model, the development of cochlea lag from 28 days on and finally lead to malformation of cochlear and degeneration of Corti's organ, which suggests that *Sox10* gene mutation directly affects the early development of cochlear organs.

In conclusion, the above model animals have made important contributions to the study of the effect of *Sox10* gene on the development of cochlear organs (BREUSKIN et al., 2009; HAO et al., 2018; LANG, 2003; YANYAN et al., 2014; TACHIBANA et al., 2003). Regarding to signal pathways, Breuskin (BREUSKIN et al., 2009) et al. found that *Sox10* protein downregulated the expression of *Jagged1* gene in a concentration dependent manner, causing apoptosis of cochlear sensory progenitor cells. Notch signaling pathway mediated by *Jagged1* gene regulates the development of sensory progenitor cells, which is indispensable to the regeneration and replacement of Sertoli cells in mammals (KIERNAN et al., 2006; PAN et al., 2010).

In the *Sox10*<sup>p.r109w</sup> mutant miniature pig model, inner ear tissue transcriptome sequencing shows that in the early stage of embryonic development, genes regulated by *Sox10* are *Wnt1*, *Pax 6*, *fezf1*, *KCNQ4* (BURTON et al., 2004). *Sox10*<sup>p.r109w</sup> mutant miniature

pig is a good model to study how *Sox10* gene regulates the development of inner ear, but there are also limitations. If cochlear system and vestibular system could be separately studied, it would be more meaningful. Compared with rodents, *Sox10* gene is more widely expressed in human fetal and adult tissues, which is not limited within glial cells of the central nervous system, and it plays a more significant role in the human physiological development (PUSCH et al., 1998; Owen et al., 2016; WATANABE et al., 2000; BONDURAND et al., 1998). Rodent models cannot well exhibit the development of human cochlea. Miniature pigs are large mammals, and the development and morphology of cochlea are more similar to humans (GUO et al., 2017; ZHONG et al., 2018), so *Sox10*<sup>p.r109w</sup> mutant Waardenburg miniature pig model can better simulate how *Sox10* leads to Waardenburg in vivo. For a complex disease, a more detailed understanding of the pathogenesis and what signaling pathways mediate are important for effective treatment (ZHU et al., 2020).

### 5. Conclusion

Sensorineural deafness and balance dysfunction are common sensory disorders, which seriously affect the quality of people's life and bring a heavy burden to individuals, families and the society. With the progress of research, genetic factors are found more and more important in etiology. Since the discovery of *Sox10* gene in 1993, its structure and function have been widely studied. As the main pathogenic factor of Waardenburg, *Sox10* gene has been deeply studied in the peripheral nervous system and melanocytes, but its function in inner ear still needs to be explored. Due to special anatomy and important function of inner ear, experiment on pathogenic mechanism cannot be conducted clinically, only case observation and image diagnosis can be carried out.

At present, the research on pathogenic mechanism is mainly conducted in vitro. Therefore, animal models play an irreplaceable role in the discovery, functional verification, diagnosis, prevention and treatment of inner ear pathogenic genes. In the future, by exploring the function of *Sox10* protein as a transcription factor at different stages of inner ear development, the ability of *Sox10* protein to bind target gene promoters, and verifying them in animal models, especially in miniature pigs, we can better understand the molecular mechanism regulated by *Sox10* gene in the development of inner ear.

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