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Transcription factors in the development of inner ear hair cells

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1. ABSTRACT

Inner ear hair cells are the sensory receptors that detect and convert sound vibrations and head movements into neural signals. However, in humans, these cells are unable to regenerate if they are damaged or lost. Over thepast decade,there has been an exponential increase in interest and progress in understanding of the development of the inner ear and of hair cells, aiming to gain insights into hair cell repair or even regeneration. In hair cell development, various transcription factors have been found to be involved in the processes of hair cell proliferation, differentiation and survival. Among these transcription factors, Math1, Gata3, Sox2 and Atoh1 have been highlighted for their crucial role in the fate of hair cells. In this article, we will summarize the current understanding of the role of transcription factors in hair cell development, focusing on the role and possible mechanisms of Math1, Gata3, Sox2 and Atoh1.

2. INTRODUCTION

The inner ear is a complex structure with functions of sound detection and balance. Impaired development of the inner ear leads to hearing or balance disorders. A transcription factor is a key protein in the transformation of genetic information, binding to DNA and then controlling its transcription to messenger RNA, and thus participating in various important cellular processes (1). Several transcription factors participate in regulating the development of the inner ear, even from the embryonic stage (2-7). Among the various types of cells in the inner ear, hair cells are the sensory receptors that detect and convert sound vibrations and head movements into neural signals (8,9). However, hair cells lack the capacity to regenerate in humans if they are damaged or lost (10). Reviewing the key transcription factors that participate in the survival, differentiation or proliferation of hair cells may provide insights into hair cell regeneration.

3. TRANSCRIPTION FACTORS ININNER EAR DEVELOPMENT

The inner ear is derived from the otic placode, an epithelial structure which forms part of the surface non-neural ectoderm adjacent to the caudal part of the hindbrain (11,12). In the otic placode, transcription factors Fgf3, Fgf8 and Pax2are essential for itsspecification (13,14). Moreover, Wnt signaling canspecify otic placode by upregulating otic genes or by upregulating the Notch signaling pathway, which than provides positivefeedback to Wnt signaling (15). Another example is that Sox9, the high mobility group (HMG)-domain-containing transcription factor, controls adhesive properties and invagination of placodal cells in a cell-autonomous manner, and maintains the progenitors in the otic epithelium (16,17).When these factors were abnormal, the inner ear may develop alloplasiaduring the early stages.

In different parts of the inner ear, differenttranscription factors are involved in development. In the semicircular canals, the nuclear receptors Nor-1 and Gbx2 are essential for proliferation or differentiation (18,19), whereas inthe vestibulum, BETA2/NeuroD1, Fkh10 and Pax2 transcription factors are involved in its development (20-22). Pax2 not only

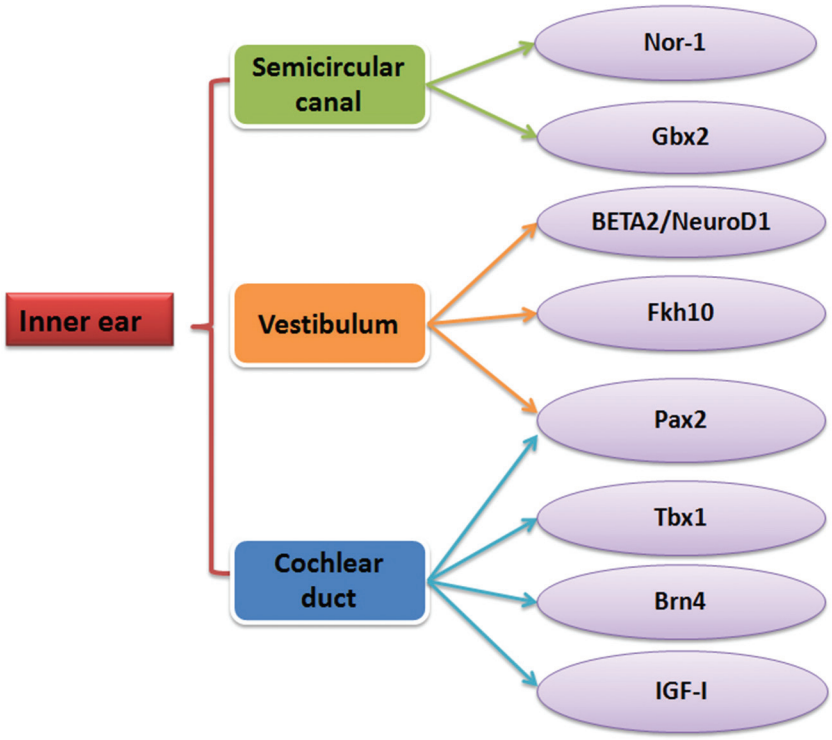

Figure 1. Transcription factors in different aspects of inner ear development. Nor-1 and Gbx2 are essential for semicircular canal development. MeanwhileBETA2/NeuroD1, Fkh10 and Pax2 transcription factors are involved indevelopmentof the vestibulum. Pax2 not only participates in development of the vestibulum, but also in cochlear duct development. The development of the cochlear duct also involves factors such as Tbx1, Brn4 and insulin-like growth factor (IGF)-I.

participates in development of the vestibulum, but is also essential in regulating differentiation during cochlear duct development (23,24). In contrast, development of the cochlear duct involves factors such as Tbx1, Brn4 and insulin-like growth factor (IGF)-I (25,26) (Figure 1). IGF-I also participates in the survival and differentiation of sensory cells and otic neuroblasts (26,27). Moreover, sensory cells can also be regulated by Rbpj, Hedgehog, Foxi2 and Foxi3 (28-30). Thus, the survival, differentiation and proliferation of cells in the inner ear involve several transcription factors. In addition to its role insensory cells, STOX1 regulates proliferation of epithelial cells via the AKT pathway (31), and Tfap2a promotes specification and maturation of neurons (32).Therefore, transcription factors can participate in development of the inner ear by regulating survival, differentiation and proliferation of different types of cells.

4. TRANSCRIPTION FACTORS IN HAIR CELL DEVELOPMENT

In the development of hair cells, the POU-domain factor Brn-3c is essential for hair cells to acquire auditory and vestibularfunctionsduring the late embryonic and early postnatal period (33). On the other hand, the development of hair cells can be inhibited by the transcription factor RY-box containing gene 2, whereas the motor protein myosin II can regulate extension of the organ of Corti and the alignment of hair cells (34).

Furthermore, several transcription factors regulate the differentiation of hair cells, such as repressor element-1 silencing transcription factor, six1 (35,36). Among the factors involved in celldifferentiation, Pax2 is an early marker of hair cells (37). As an architectural transcription factor, Hmga2 is also tissue-specifically expressed in early development ofthe cochlea, and may have a dual role in regulating hair cell differentiation and maintenance that is predominantly expressed in embryonic hair cells, but is downregulated in the cochlear epithelium of postnatal ears (38).On the other hand, the survival of hair cells can be promoted by the anti-apoptotic factor z-Val-Ala-Asp-fluoromethylketone in a mouse model of deafness (39). Similarly, the LIM-homeodomain transcription factor Isl1 was also found to play a role of maintaining hair cell survival (40,41). Interestingly, the zinc finger transcription factor Gfi1, atarget of the Pou4f3 deafness gene, is essential not only for differentiation of hair cells but also for their survival (42,43), suggesting a crucial role of Gfi1 in hair cell development and degeneration.In addition to Gfi1, Nr2f2 is another target of Pou4f3 and is also related to hair cell development and survival (44).

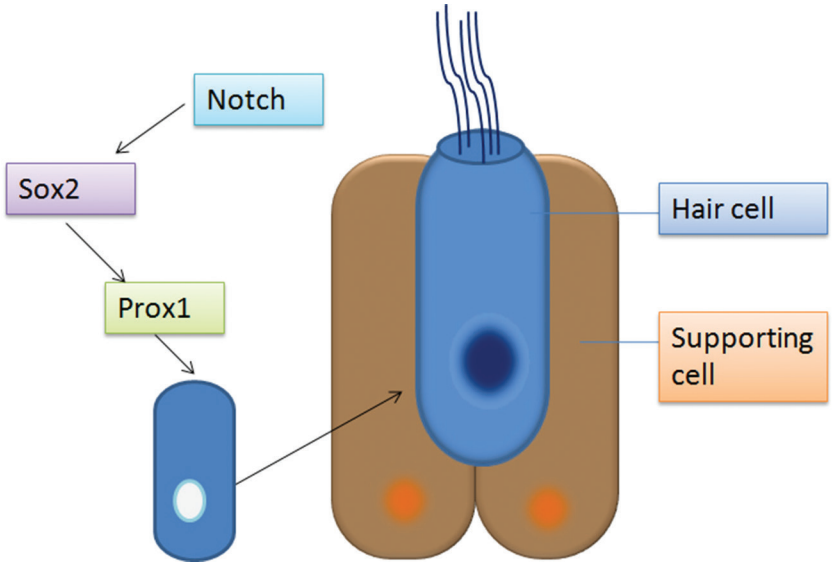

Figure 2. Sox2 in hair cell differentiation. Sox2 expression ispositively regulated by Notch signaling and then targets Prox1. Decreased expression of Sox2 leads to precocious hair cell differentiation and over- production of hair cells in theinner ear.

These findings illustrate the crucial roletranscription factors play during hair cell development, from differentiation to survival. Among the various transcription factors, Math1, Gata3, Sox2 and atonal homolog 1 (Atoh1)haveattracted much attention for their crucial roles in hair cell development. Here, we will discuss recent findings on their role and possible mechanisms in hair cell development.

4.1. Math1 in hair cell development

Math1, the basic helix-loop-helix transcription factor, plays an essential role in controlling the generation of all elements of the proprioceptive pathway, including hair celldevelopment (45,46). It regulatesformation of the sensory epithelia by initiating both inductive and inhibitory signaling in the development of the cochlea (47). Furthermore, Math1 is a key factor in inducing differentiation of hair cells from embryonic stem cells (48). Recently, a study on neonatal mice showed that Math1 caninduce hair cell-like cells to proliferate and differentiate in the lesser epithelial ridge (49). Thus, Math1 may be crucial in promotingthe proliferation and differentiation of hair cells even from the embryonic stage. Although the upstream regulator of Math1 is known to be Sox2 (50), better understanding of the upstream and downstream mediators of Math1 is needed to further elucidate the mechanism of Math1 regulation in hair cell development.

4.2. Sox2 inhair cell development

Sox2 is a member of the Sox family of transcription factors and is similar toSox9in that it contains an HMG-domain. It is essential in maintenance of embryonic and neural stem cells and is responsible for progenitor self-renewal and commitment. The impaired function of Sox2 leads to defects of ear sensory epithelia.As mentioned above, Sox2 has been found to act upstream of Math1 in regulating the development of sensory organs in the inner ear (50). In a study of chick inner ear, Sox2 protein was found to be expressed in aspatially- and temporally-restricted manner throughout ear development, and is transiently expressed in embryonic hair cells (51). In development of the inner ear sensory cell, Sox2 can specify sensory progenitors and drive development of the sensory cell progenitors in the inner ear (52). Furthermore, Dabdoub and colleagues identified diverse roles of Sox2 in the development, specification, and maintenance of sensory cells (53). They observed that mutations in SoX2 could lead to sensorineural hearing loss. Meanwhile, decreased expression of Sox2 cancause precocious hair cell differentiation and an over-production of inner hair cells. Sox2 expression was positively regulated by Notch signaling, and subsequentlytargetedProx1, a homeobox transcription factor (53). In addition, a surprising finding was that Sox2 could trigger an incoherent feed-forward loop in hair cell differentiation. It directly activates Atoh1 through itstranscriptional activator function, whereas it also promotes the expression of Atoh1 negative regulators (54). This finding suggests a complex role of Sox2 in hair cell differentiation, which may be a key factor connecting different signaling pathways during the process of cell differentiation.

4.3. Atoh1 inhair cell development

Atoh1 is a member of the basic helix-loop-helix family of transcription factors. Atoh1 is expressed in progenitors that may differentiate into hair cells and participates in hair cell development (55,54). Deletion of Atoh1 leads to impaired differentiation ofhair cells andloss of most of the organ of Corti, suggesting the essential role of Atoh1 in inner ear hair cell formation (56).

Atoh1 mutation, namely Atoh1(trhl), leads to hair cell loss in the inner ear (57). Atoh1 is also essential for development of hair cell mechanotransduction, viability, and maintenance such that reduction or deletion of Atoh1 leads to progressive loss of almost all the inner ear hair cells, as well as the majority of the outer hair cells (58). Lin and colleagues reported an exciting finding thatAtoh1 can induce mesenchymal stem cells to transform into hair cell-like cells whenco-cultured with spiral ganglion neurons (59), which may provide insights into hair cell regenerationand deafness therapy.

4.4. Gata3 inhair cell development

Gata3 belongs to the Gata family of transcription factors, which usually is essential in the differentiationof epithelial cells and T cells (60,61). In inner ear development, Gata3 plays a crucial role and haploinsufficiency leads to hearing loss even in early postnatal development, which ismaintained through to adulthood (62). Milo and colleagues subsequently found that the function of Gata3 during inner ear development may be associated with IGF signaling and AKT signaling. GATA3 deficiency leads to decreased expression of IGF1, IGF2, and several IGF-binding proteins as well as the serine-threonine kinase Akt2/PKBbeta, but to increased expression of Akt1/PKBalpha protein (63) (Figure 2). In cochlear development, Gata3 isthought to be essential for neurosensory specification and differentiation. Gata3deficiency leads to impaired differentiation ofhair cells, with decreased hair cell differentiation in the mouse cochlea (64,65). However, the way in which Gata3 participates inhair cell differentiation is largely unknown. Further study on this mechanism will provide a better understanding of hair cell differentiation.

5. CONCLUSIONS

Hair cells are essential for the functions of hearing and balance in the inner ear. The past decade has seen exponential increases in interest and progress in the field of hair cell development. In this field, various transcription factors have been found to be involvedin the processes of hair cell proliferation, differentiation and survival. As we have discussed, Math1, Gata3, Sox2 and Atoh1 have been better investigated than other transcription factors. These factors are crucial in determining the fate of hair cells. Atoh1 can even induce hair cells to differentiate from mesenchymal stem cells. These findings provide insight into hair cell regeneration. The challenge in future is how to intervene to regulate or even control the fate of hair cells. The future is exciting in terms of the benefits for deafness patients that may emerge as a result ofhair cell regeneration.

6. ACKNOWLEDGEMENTS

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Abbreviations: HMG: high mobility group; IGF: Insulin-like growth factor

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