Review

Modeling human congenital disorders with neural crest developmental defects using patient-derived induced pluripotent stem cells

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ABSTRACT

The neural crest is said to be the fourth germ layer in addition to the ectoderm, mesoderm and endoderm because of its ability to differentiate into a variety of cells that contribute to the various tissues of the vertebrate body. Neural crest cells (NCCs) can be divided into three functional groups: cranial NCCs, cardiac NCCs and trunk NCCs. Defects related to NCCs can contribute to a broad spectrum of syndromes known as neurocristopathies. Studies on the neural crest have been carried out using animal models such as \textit{Xenopus}, chicks, and mice. However, the precise control of human NCC development has not been elucidated in detail due to species differences. Using induced pluripotent stem cell (iPSC) technology, we developed an \textit{in vitro} disease model of neurocristopathy by inducing the differentiation of patient-derived iPSCs into NCCs and/or neural crest derivatives. It is now possible to address complicated questions regarding the pathogenetic mechanisms of neurocristopathies by characterizing cellular biological features and transcriptomes and by transplanting patient-derived NCCs \textit{in vivo}. Here, we provide some examples that elucidate the pathophysiology of neurocristopathies using disease modeling via iPSCs.

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1. Neural crest development during embryogenesis

The neural crest originates from the neural tube and gives rise to various bodily tissues, including nerves, glial cells, bones, cartilage,
fat, and connective tissues. The neural crest was presumably first identified by Wilhelm His in 1868 [1], and the evolutionary emergence of the neural crest is a characteristic of vertebrate embryos. Neural crest-derived cells are incorporated into many parts of the vertebrate body in addition to the ectoderm, mesoderm and endoderm. Neural crest cells (NCCs) leave their original location in the dorsal neural tube and migrate to various organs according to their predetermined cell fate, and they can differentiate into neural and mesenchymal cell types [2,3]. Because NCCs are distributed among various organs, they are regarded as the fourth germ layer, thereby enhancing the complexity of the vertebrate body [4].

During the early phase of vertebrate development, NCCs migrate from the dorsal area of the hindbrain along predefined paths in the developing embryo to invade various tissues and organs, wherein they produce a variety of neural crest derivatives [2] (Fig. 1). The neural crest can be divided into five functional domains along the anterior–posterior axis that give rise to the cranial neural crest, cardiac neural crest, vagal neural crest, trunk neural crest and sacral crest. Particularly, in the head region of mammals, cranial NCCs explicitly differentiate into various cell types, including osteocytes, chondrocytes, smooth muscle cells and pericytes, tendon cells, dermal cells, other connective tissue cells, adipocytes, stromal and endothelial cells in the cornea, and odontoblasts [2,5–7]. Some of these cells are also known to be differentiated from mesoderm-derived mesenchymal cells originating at other sites. During dorsolateral migration, the differentiation of NCCs is thought to be influenced by signals arising from multiple sources. Cranial NCCs are divided into two different groups based on the Eph/ephrin and semaphorin signaling pathways, whose distributions vary across species. Eph/ephrin signaling is vital for the generation of regions in which NCCs are absent or for directing individual subpopulations of NCCs to specific migration pathways [8]. Semaphorins are important for partitioning the NC population into subgroups and may attract some specific NCCs to particular locations. They may directly interact with the ectoderm as they migrate through the extracellular matrix (ECM) microenvironments in the head [9].

**Fig. 1.** Overview of NCCs differentiation along the anterior–posterior axis of the embryo. Only cranial NCCs can differentiated into bone and cartilage in addition to melanocyte, cranial neurons and glial cells and odontoblasts. Cardiac NCCs migrate into 3rd-6th pharyngeal arches and give rise to aorticopulmonary septum, smooth muscle of the aorta and pulmonary artery and valvular tissue and cardiac neurons. Vagal and Sacral NCCs consists of enteric nervous system. Trunk NCCs migrate dorsolateral and ventrolateral. The former group give rise to melanocyte and the latter give rise to chromaffin cells, known as endocrine cells in adrenal glands, and the neurons of the sympathetic nervous system.
2. **What is 'neurocristopathy'?**

After NCCs are induced, they delaminate from their origin and migrate to specific locations, where they then differentiate into neural crest derivatives. The formation of the neural crest requires temporospatially programmed inputs consisting of intercellular signals and cues from the surrounding environment. Defects related to the proliferation, specification or differentiation of pre-migratory NCCs that comprise dorsal progenitor cells, which delaminate from the neural plate border and migrate ventrally, could contribute to a broad spectrum of syndromes known as neurocristopathies, as named by Robert P. Bolande in 1974 [10,11].

Abnormalities in the emergence and timing of neural crest-related signals lead to a set of syndromes called neurocristopathies. Even small changes in the external cues that control the migration of NCCs can affect their migration and differentiation patterns, and the defective migration of cranial NCCs results in significant morphological abnormalities in the face and neck [12]. Defects in melanocytes, which are also neural crest derivatives, cause piebaldism and defects in Meissner’s and Auerbach’s nerve plexuses, resulting in Hirschsprung disease (HSCR). Autonomic nervous system defects cause familial dystautonomia. Multiple defects in neural crest derivatives can result in multiple congenital anomaly disorders, such as CHARGE syndrome, Waardenburg syndrome, chromosome 22q11.2 (chr.22q11.2) deletion syndrome, craniofrontonasal syndrome and Axenfeld-Rieger syndrome. Furthermore, some cancers, such as pheochromocytoma, paraganglioma, multiple endocrine neoplasia (MEN), neurofibromatosis type I and melanoma, are also known to arise from neural crest defects.

3. **Disease modeling of neurocristopathies using induced pluripotent stem cells (iPSCs)**

The diseases that have been incorporated as neurocristopathies are mainly based on findings associated with neural crest derivatives. The usefulness of this definition is based on its ability to provide an etiological origin for certain tumors and/or congenital malformation associations that are otherwise difficult to classify by other means. To clarify the definition of each disease, we can generate cells related to the pathological mechanisms using iPSCs. To improve the understanding of the pathogeneses of neurocristopathies, many previous studies have used iPSC technology, which was invented by Shinya Yamanaka in 2006 [13] and has enabled researchers to convert somatic cells into pluripotent cells.

Using this technology, we are able to generate disease-specific differentiated cells, such as NCCs and/or neural crest derivatives. It is now possible to investigate complicated questions regarding cell biology, transcriptomics and *in vivo* transplantation that are related to the pathogeneses of different disease states. We can also perform pharmacological studies, and the development of *in vitro* and *in vivo* models of human neural crest migration has made it possible to construct a system for screening drugs that improve the defective migration of NCCs in neurocristopathies. The neural crest is known to contribute to not only craniofacial morphogenesis, as mentioned above, but also enteric ganglion (Auerbach’s and Meissner’s plexuses) adrenalin-producing cells in the adrenal medulla, and sympathetic neurons, among others. This method will presumably be applicable for the identification of drugs to treat patients with these disorders. Here, we describe some examples of iPSC-based neurocristopathy modeling (Table 1).

### Table 1

| Methods for disease modeling of neurocristopathy and other neural crest-related events using hPSCs. | How populations of interest are induced from hiPSCs | Summary of the outcomes | Ref. |
|---|---|---|---|
| **Rescue of Hirschsprung disease model mice by grafting human enteric NCCs** | Human pluripotent stem cells (hiPSCs) are differentiated into vagal/enteric neural crest cells (NCCs) via dual SMAD inhibition, WNT activation and RA treatment. | Extensive migration of grafted hiPSCs-derived enteric NCCs rescued disease-related mortality in Hirschsprung disease mice. | [19] |
| Disease modeling for Craniofrontonasal syndrome (CFNS) | hiPSCs are differentiated into neuroepithelial cells, prior to neural crest cells (NCCs) emigration from neural tube, via dual SMAD inhibition. | hiPSCs-based modeling of CFNS supported that phenotypes of the disease is caused by cellular interference due to the mosaicism for mutated EPHRIN-B1 expression by random X inactivation in heterozygous females, showing robust cell segregation of neuroepithelial cells. | [32] |
| In vitro modeling of human heart development using hPSCs | hESC are differentiated into first heart field (FHF) and second heart field (SHF) progenitors in a week via ACTIVIN, WNT3A and BMP4 activation. FHF progenitors are isolated as HCN4(-) cells by flowcytometry. SHF progenitors are ESI1(+). | OE1(+). | [27] |
| Disease modeling for neurofibromatosis type I | hiPSCs are differentiated to P75/HNK1 (+/-) NCCs via dual SMAD inhibition, and subsequent WNT activation. Then, these iPSCs-derived NCCs are further differentiated into Schwann cells. | NFI(-/-). | [33] |
| Disease modeling for CHARGE syndrome | hiPSCs are differentiated into P75/HNK1 (+/-) NCCs using the following two different methods: 1) hiPSCs are neurally differentiated via dual SMAD inhibition. 2) Neurospheres are prepared from hiPSCs and spontaneously attach to the petri-dish after day 6–8. P75/HNK1 (+/-) cells start to migrate out from the rosettes. | Defective migration of hiPSCs-NCCs from CHARGE patients were observed by the in vitro and in vivo assays. | [37] |

hPSC: human pluripotent stem cells, hiPSC: human induced pluripotent stem cells, hPSCs; human pluripotent stem cells, FHF: first heart field, SHF: second heart field, neural crest cells: NCCs, NF1: neurofibromatosis type I.
Mowat-Wilson syndrome, MEN2, Waardenburg syndrome, and familial dysautonomia, are also known to be associated with the etiology of HSCR. The molecules encoded by these genes have also been reported to be involved in the signaling pathways essential for ENS development [15,17,18].

EDNRB \textsuperscript{-/-} human embryonic stem cell (ESC)-derived enteric NCCs show defective migration in vitro. A drug screening performed using 1280 FDA-approved compounds with this in vitro model showed that pepstatin-A, an inhibitor of acid proteases, rescued the defective migration observed in HSCR mice, and BACE2 was identified as a potential pepstatin target. Drugs related to this mechanism may prevent aganglinosis during embryogenesis and/or repair postnatal enteric neuron function [19].

H. Yuan et al. reported that the premigratory neural crest, which has not migrated into the gut, can form enteric neurons and mediate motility in the mouse gut [20]. The transplantation of these cells into the intestines of HSCR mice lacking peristalsis due to aganglionosis, as in Hirschsprung’s disease, promotes their survival and migration into the colon, thereby prolonging mouse survival [19]. Furthermore, Li et al. reported that small intestinal organoids containing NCCs cocultured with smooth muscle layers of ganglionic gut tissue contributed to intestinal peristalsis upon implantation [21]. This result suggests the feasibility of treating diseases that disrupt the intestinal tract, such as HSCR, with regenerative medicine.

3.2. Chromosome 22q11.2 deletion syndrome (including DiGeorge syndrome)

Due to the presence of low-copy repeats at both ends of the deletion region on chr.22q11.2, the common 1.5–3.0 Mb deletions are more likely to occur in patients with chr.22q11.2 deletion syndrome due to mismatches during chromosomal recombination [22] (Fig. 2). This syndrome is characterized by cardiac outflow tract defects, facial anomalies, hypoplasia of the thymus, cleft palate and hypoplasia of the parathyroid. In 1965, Dr. Angelo DiGeorge reported an infant with thymic dysplasia and hypoparathyroidism. This was named DiGeorge syndrome. Later, it was discovered that chromosomal deletions in the 22q11.2 region can cause a series of various symptoms, not necessarily thymic dysplasia and hypoparathyroidism, and the term 22q11.2 deletion syndrome was coined [23]. These abnormalities result from defects in the development of embryonic pharyngeal arches and pouches. Ablation of the cephalic neural crest in OVO reportedly results in symptoms similar to those of chromosome 22q11 deletion syndrome [24]. Abnormal neural crest development in pharyngeal arches is believed to be the primary cause of the syndrome. Based on transgenic mouse models, haploinsufficiency of TBX1, located on chr.22q11.2, is likely the major determinant of aortic arch defects in patients with this syndrome [25]. However, TBX1 is not expressed in the neural crest during pharyngeal arch development in mouse embryos [26], suggesting that inappropriate epithelial-mesenchymal signaling caused by TBX1 haploinsufficiency may affect the migration and differentiation of NCCs during pharyngeal arch development [18,19,26]. The neural crest and the cardiac outflow tract can be differentiated from human iPSCs [27]. It is now possible to study how genes in the chr.22q11.2 region are related to the disease phenotypes in more detail. Adults with this syndrome are at an extremely high risk of developing schizophrenia [28]. Many researchers have utilized patient-derived iPSCs to explore the mechanisms underlying this schizophrenic phenotype [29–31].

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Fig. 2. Schematic overview of genes in the 22q11.2 critical region. Schematic overview of 3 Mb in the 22q11.2 region. The gray columns A, B, C, D indicate blocks of low-copy repeats, named LCR22s. Breakpoints of the deletion mostly occur in these LCR22s. Eighty-five percent of patients with chr.22q11.2 deletion syndrome have a 3 Mb deletion, and 5% harbor a 1.5 Mb deletion. Forty-four coding genes and 9 noncoding genes are located in this region. The genes listed in blue were reported to be associated with schizophrenia. TBX1 (shown in red) is known as a cardinal gene of chr.22q11.2 deletion syndrome. Eight coding genes were reported to cause autosomal recessive syndromes. ND: neural development, NC: neural crest, PA: pharyngeal arches.
Interestingly, Bundo et al. showed that the retrotransposition of long interspersed nuclear element-1 (LINE-1), a class I transposable element, was increased in neuronal cells differentiated from iPSCs derived from patients with chr.22q11 deletion syndrome [23]. iPSC technology is valuable for exploring other phenotypes caused by neural crest defects in patients with chr.22q11.2 deletion syndrome.

### 3.3. Craniofrontonasal syndrome

This syndrome is characterized by craniofacial, skeletal and neurological anomalies caused by EFNB1 mutations on chromosome X. EFNB1 encodes a ligand of ELK (EPHB1) and is expressed in the frontonasal neural crest. Interestingly, heterozygous female patients show a more severe phenotype than hemizygous males, who typically present with only hypertelorism. This phenomenon is thought to involve cellular interference of the functional mosaicism of EPNB1 due to X chromosome inactivation in females. Nießhammer T. et al. differentiated hiPSCs into human neuroepithelial (hNE) cells, which express PAX6, SOX1 and OTX2, using a monolayer dual-SMAD inhibition protocol. They showed that EPHB1-expressing (wild-type) and EPHB1-nonexpressing (patient-derived) cells segregated to form ectopic boundaries in mixed cell cultures, thus mimicking EPHB1 mosaicism [32].

### 3.4. Neurofibromatosis type 1 (von Recklinghausen disease)

Neurofibromatosis type 1 (NF1) is an autosomal dominant tumor predisposition syndrome caused by mutations in the gene encoding NF1, a negative regulator of the RAS pathway. The biallelic inactivation of NF1 gene causes the proliferation and malignant transformation of neural crest derivatives, resulting in pathologies such as plexiform neurofibromas (PNFs), which are benign Schwann cell (SC) tumors of the peripheral nerve sheath. Carrio et al. generated PNF-derived NF1(−/−) iPSCs and showed that their genomic status enabled their differentiation toward neural crest stem cells and then to stem cells. iPSC-derived NF1(−/−) iPSCs and showed that their genomic status enabled their differentiation toward neural crest stem cells and then to stem cells. iPSC-derived NF1(−/−) iPSCs exhibited a high proliferation rate, a poor capacity for myelination, and a tendency to form 3D spheres [33].

### 3.5. CHARGE syndrome

CHARGE syndrome is a genetic disorder characterized by a constellation of nonrandomly associated malformations, i.e., coloboma, heart defects, atresia choanae, retardation of growth and development, genitai hypoplasia, and ear anomalies/deafness.

A previous study showed that CHD7 regulates chromatin formation and the expression of downstream genes by binding to genomic DNA [34]. Defects in the cranial neural crest are thought to lead to the features of CHARGE syndrome, but this has not been directly demonstrated [34]. Bajapai et al. showed that knocking down CHD7 in human ESCs resulted in migratory neural crest formation defects, thereby leading to this hypothesis [35]. NCCs are thought to be the primary cells affected in CHARGE syndrome [36]. Our group showed the defective migration of iPSC-NCCs derived from CHARGE patients using transcriptome analysis and in vitro and in vivo migration assays [37] (Fig. 3A). A mixture of control and CHARGE iPSC-NCCs was transplanted into the dorsal hindbrains of chick embryos (HH stage 8–10). Notably, the transplanted iPSC-NCCs had migrated in the expected direction to the ventral area, similar to NCC migration in normal embryos, at 36 h after transplantation. A comparison of the migratory pathways of control and CHARGE iPSC-NCCs in identical embryos revealed that the CHARGE iPSC-NCCs exhibited a similar or less extensive migration pattern than the co-transplanted control iPSC-NCCs (Fig. 3B). Furthermore, transcriptome analysis revealed that almost 60% of the genes that were differentially expressed between the control and CHARGE iPSC-NCCs were listed as target genes of CHD7 in the ChIP-seq datasets obtained from the ENCODE transcription factor target database [38] (Fig. 3C). It is therefore reasonable to suggest that CHD7 regulates the craniofacial phenotype of CHARGE syndrome.

### 4. Conclusion and perspectives

It is currently impossible to examine the mechanisms of human neurocristopathies due to technical challenges and ethical concerns surrounding the collection of NCCs from human embryos. Moreover, the regulation of developmental gene networks in NCCs is known to...
vary among species [39]. NCCs derived from patient-derived iPSCs are an appropriate source for modeling the human cellular features of each disease in vitro. We can also perform drug screenings for diseases related to the neural crest, such as HSCR [39]. These in vitro disease models have become a powerful assay system for evaluating NCC dysfunction in not only neurocraniopathies but also infants with toxic exposure to factors such as vitamin A and alcohol, which affect neural crest development [40]. NCCs play important roles in the formation of various organs, and some congenital neurocraniopathies are caused by reproductive toxicity. Deformities in experimental animals caused by NCC deficits have been explored by assessing the toxicity of newly developed drugs. The iPSC-NCC system presented herein could be used as an animal-free NCC system for reproductive toxicity testing. In addition, it was reported that neural crest-derived fibroblasts are erythropoietin-producing cells in the kidney and are involved in kidney fibrosis in chronic kidney disease [41]. Chronic renal failure is exploding in developed countries, and in vitro neural crest studies can be expected to be useful in exploring ways to treat these diseases.

Declaration of competing interest

H.O. is a founding scientist and scientific advisor of SanBio Co. Ltd. and K Pharma Inc. Other author indicates no potential conflicts of interest.

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