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SOX10 in Neurodevelopment and Disease: Molecular Mechanisms, Pathological Models and Therapeutic Prospects

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Abstract: SOX10 is a neural crest transcription factor that preserves lineage competence and guides differentiation. Because it functions in enteric progenitors, Schwann cells, melanocytes, and auditory-supporting cells, reduced activity can produce multisystem disease. This review links SOX10-centered regulation to Waardenburg syndrome, Hirschsprung disease, deafness, and glial dysfunction, and highlights models that support mechanism-based therapy design.

Keywords: Neural crest; Neurocristopathy; Hirschsprung disease; Waardenburg syndrome; Schwann cell biology; Inner-ear homeostasis; Precision medicine

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1. Introduction

SOX10 should not be treated only as a marker used to identify neural crest derivatives. After neural crest induction at the neural border, it helps maintain migratory neural crest cells and later contributes to enteric, glial, melanocytic, and auditory-supporting lineages [1–4]. In this sense, the main developmental task of SOX10 is to keep cells competent while allowing differentiation to occur at the appropriate stage and tissue site [1,4,5].

This developmental role explains why pathogenic SOX10 variants rarely produce a single isolated phenotype. Since the first association between SOX10 mutations and Waardenburg-Hirschsprung syndrome, subsequent work has described combined defects in tissues that share neural crest ancestry [6-8]. The following sections. Therefore, focus on three connected issues: the regulatory circuits involving SOX10, the multisystem pathology that follows SOX10 disruption, and the model systems that may support intervention guided by mechanism rather than by phenotype alone.

2. Molecular architecture and regulatory logic of SOX10

SOX10 is a SOXE-family factor whose HMG domain bends DNA and shapes transcriptional responses [1]. Induced downstream of WNT, BMP, and FGF signals, it stabilizes a neural crest program that remains plastic but lineage-committed [2,3]. SOX10 thus links transient border signaling to durable developmental identity [1-3].

The specificity of SOX10 action depends strongly on its transcriptional partners. In pigment cells, it participates in MITF-centered networks; in enteric progenitors, it is linked to RET-associated modules; and in glial lineages, it converges with EGR2/KROX20-related myelination circuits [9-14]. Disease may therefore reflect reduced dosage or failed enhancer engagement in a given lineage, explaining overlapping but non-identical combinations of aganglionosis, deafness, pigmentation defects, and glial dysfunction [6,10-12,7].

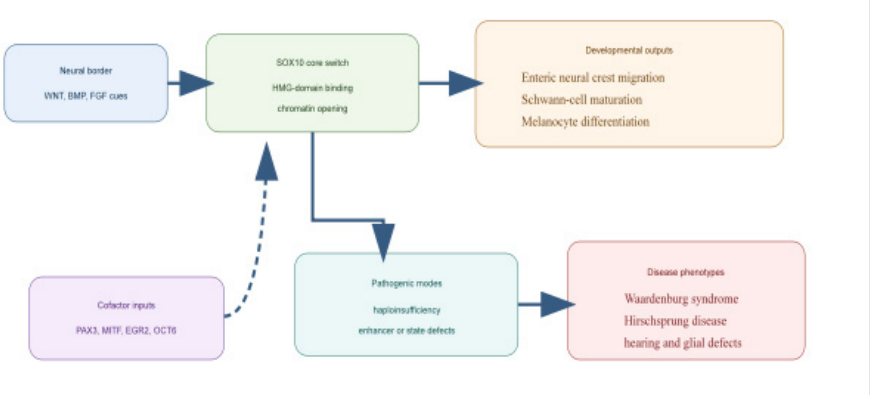

Figure 1. SOX10-centered regulatory logic linking neural crest developmental programs with representative disease phenotypes [1–5,6,15,9,20,7,16].

3. SOX10 in neural crest and neuroglial lineage allocation

3.1. Multipotency, migration, and enteric colonization

SOX10 preserves neural crest multipotency while limiting premature neuronal differentiation, allowing progenitors to migrate and remain competent [4]. In enteric lineages, even partial disruption can impair colonization enough to produce distal aganglionosis [5,17,12,16].

The enteric nervous system is a strong model of dosage-sensitive SOX10 biology. Mouse and single-cell studies show that Sox10 insufficiency alters progenitor allocation and lineage trajectory, not just cell number [17,16]. SOX10-associated Hirschsprung disease, therefore, likely reflects mixed survival, enhancer, timing, and modifier effects rather than one mechanism [6,12,7,16,8].

Table 1. Core developmental modules controlled or interpreted by SOX10

Developmental context	Principal regulatory logic	Representative consequence of perturbation	Key references
Neural border to premigratory neural crest	SOX10 consolidates border-derived competence after WNT/BMP/FGF induction and stabilizes a migratory neural crest program.	Reduced lineage competence or unstable specification before widespread dispersal.	[1-3]
Multipotent migratory and enteric progenitors	SOX10 preserves progenitor identity, restrains premature neuronal differentiation, and supports RET-linked enteric programs.	Distal gut colonization failure and Hirschsprung-associated trajectory defects.	[4,17,12,16]

Developmental context	Principal regulatory logic	Representative consequence of perturbation	Key references
Schwann-cell lineage	SOX10 cooperates with stage-specific glial regulators and later with myelination circuitry such as EGR2/KROX20.	Arrest before mature Schwann-cell identity or impaired myelin-gene deployment.	[18,15,9,19]
Melanocyte lineage	SOX10 activates MITF-centered transcriptional hierarchies and pigment-cell differentiation modules.	Hypopigmentation, patchy melanocyte loss, or lineage instability.	[10-14]
Inner ear homeostasis and cochlear glia	SOX10 intersects with auditory-supporting and glial programs that maintain ionic balance and glial plasticity.	Sensorineural hearing loss and compromised reparative potential.	[20-22]

3.2. Schwann-lineage specification and myelination

In the Schwann lineage, SOX10 is required for identity and progression through precursor, immature, and myelinating states [18,15,9]. Loss-of-function studies place it at the center of maturation beyond the immature Schwann-cell stage [15]. Its activity is integrated with NRG1 signaling and partner exchange during myelination [18,9].

This function also matters in nerve repair, where Schwann cells transiently dedifferentiate and then remyelinate [18]. SOX10 thus influences both congenital glial disease and adult recovery. Engineering studies further show that SOX10 plus immobilized NRG1 can improve production of Schwann-like cells for regenerative use [19].

3.3. Melanocyte and inner-ear lineages

The melanocyte lineage clearly demonstrates context-dependent SOX10 partnership. By cooperating with PAX3 and MITF, SOX10 supports melanoblast commitment, survival, and melanogenic gene expression[10-14]. This explains why pigmentary changes in Waardenburg syndrome are developmentally central and why severity can vary by variant class [10-11,13-14,7].

Auditory phenotypes also reflect lineage-specific SOX10 dysfunction. In the cochlea, SOX10 works with SOX9 to support fluid homeostasis and hearing-related support functions [20]. Cochlear SOX10-positive glia retain plasticity in three-dimensional culture, and new AAV studies suggest targeted intervention in relevant nonsensory compartments may become feasible [20-21,8].

4. Disease mechanisms across the SOX10 spectrum

4.1. Waardenburg-Shah syndrome and Hirschsprung disease

Waardenburg-Shah syndrome is the clearest SOX10 disorder because it combines pigmentary, enteric, and auditory defects within one developmental framework. Haploinsufficiency matters, but phenotype also depends on variant type, residual activity, lineage context, and modifier background [6-7]. The syndrome is embryologically coherent yet mechanistically variable [6-8].

SOX10-associated Hirschsprung disease shows how distal aganglionosis can arise from layered developmental defects. Mouse and single-cell studies support dosage sensitivity, altered cell-state allocation, and interaction with RET/PAX3-related regulatory logic [17,12,16,8]. Precision classification will likely need lineage-level biomarkers, not variant names alone [16,8].

4.2. Auditory phenotypes, glial vulnerability, and variable expressivity

The hearing phenotype in SOX10 disease is more than generic sensorineural loss. Because SOX10 contributes to auditory-supporting neural crest derivatives and cooperates with SOX9 in inner-ear homeostasis, variants can disrupt the microenvironment needed for normal hearing [20,7]. This also helps explain coexistence with pigmentary and broader neuroglial features [20,7-8].

Variable expressivity is therefore not simply clinical noise. Small changes in remaining SOX10 activity, partner availability, or enhancer compensation may shift developmental outcomes differently in each tissue [6-8]. Therapeutic research will need assays that resolve lineage and dosage effects, rather than endpoints that combine multiple phenotypes into broad diagnostic labels.

5. Pathological Models and Precision-Medicine Platforms

Current SOX10 research depends on a wider set of experimental platforms than earlier genetic studies. Mouse models remain indispensable for examining developmental timing, tissue architecture, and whole-organ effects, particularly in enteric and glial systems [17,15,16]. But they cannot capture the full allelic diversity seen in human sequencing or subtle variant effects across human lineages [17,15,16,8].

Human pluripotent stem-cell systems help fill this gap by allowing isogenic comparison, reporter-based tracking, and controlled differentiation toward neural crest-derived lineages. SOX10 reporter iPSCs, genome editing, single-cell analysis, cochlear glial culture, and Schwann-cell engineering now provide practical tools for stratifying mechanisms and testing lineage-specific hypotheses [23,19,21].

Table 2. Model systems currently informing SOX10 pathology and translational design

Model platform	Major strength	Best-suited question	Key references
Dominant megacolon and related mouse models	Whole-organism timing and tissue architecture	How SOX10 insufficiency distorts enteric colonization and lineage allocation in vivo	[17,16]
Schwann-lineage genetic models	Direct access to stage-specific glial maturation defects	Which transcriptional transitions fail when Sox10-dependent progression is blocked	[18,15,9]
SOX10 knock-in reporter human iPSCs	Live tracking of SOX10-positive human trajectories	How human neural crest derivatives emerge, bifurcate, and respond to engineered perturbation	[23]
SOX10 plus NRG1 Schwann-engineering systems	Regenerative manufacturing relevance	How to generate functional Schwann-like cells for repair-oriented applications	[19]
Cochlear Sox10-positive glial 3D cultures	Auditory microenvironment and plasticity	Whether glial-to-neuronal conversion or rescue can be odelled in vitro	[21]
Integrated clinical-genetic neurocristopathy frameworks	Patient stratification across syndromes	How genotype, lineage, and phenotype should be grouped for precision medicine	[7-8]

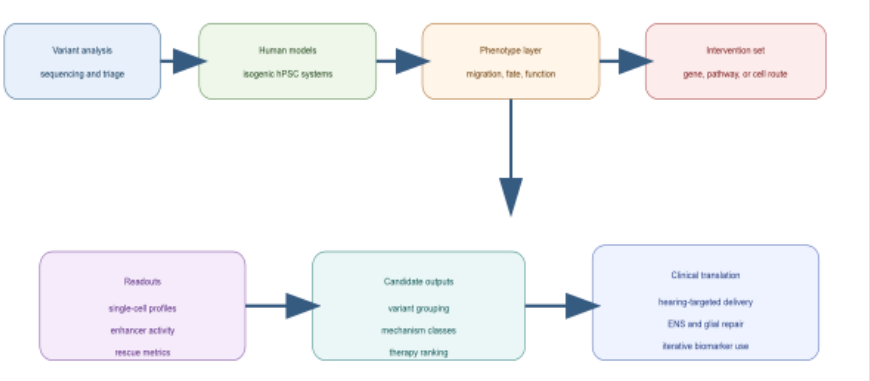

Figure 2. Mechanism-stratified precision-medicine workflow for SOX10-associated disorders, spanning variant interpretation, human modeling and therapeutic prioritization [7,16,23,19,21,8,22,24].

6. Therapeutic prospects and translational constraints

SOX10 is an attractive but difficult therapeutic target. Restoring an upstream lineage regulator could rescue multiple downstream programs, yet uncontrolled overexpression may distort fate balance or developmental timing [7-8]. Near-term gene therapy is most plausible where delivery and dosage can be locally constrained [20,7,22].

A second strategy is lineage engineering and cell replacement. SOX10 with immobilized NRG1 can guide neural crest-like cells toward Schwann-cell identity[19]. Cochlear SOX10-positive glia may also support in situ or ex vivo regenerative strategies if fate control is precise [21].

A third approach is to modulate downstream pathways rather than replace SOX10 directly. Small molecules, biologics, or restricted SOX10 delivery could stabilize selected programs while reducing the risk of broad fate perturbation. Exosome-mediated Sox10 loading in demyelination models provides proof of concept for SOX10-centered cargo delivery [24]. Treatment will likely require lineage-specific, mechanism-stratified strategies rather than a universal SOX10 therapy[7,19,21,8,22,24].

Table 3. Emerging intervention concepts for SOX10-associated disease

Intervention concept	Rationale	Current status	Major caveat	Key references
Local gene augmentation or editing	Could restore upstream lineage control in accessible tissues.	Conceptually attractive; delivery feasibility improving in the auditory field.	Narrow therapeutic window and lineage-specific dosage risk.	[7-8,22]
Pathway-guided rescue without full SOX10 replacement	May stabilize downstream programs while avoiding global fate perturbation.	Mechanistically plausible but not yet standardized clinically.	Requires precise knowledge of variant- and lineage-specific failure points.	[12,7-8]
SOX10-guided Schwann-cell engineering	Recreates developmental logic for peripheral nerve repair.	Supported by recent differentiation studies.	Cell identity, durability, and manufacturing reproducibility remain unresolved.	[19]
Auditory glial plasticity or local regenerative conversion	Targets Sox10-positive cochlear support populations with reparative intent.	Early-stage experimental evidence in 3D systems and delivery studies.	Functional integration in vivo remains unproven.	[21-22]
Restricted SOX10 cargo delivery (e.g., exosomal)	Allows transient or compartmentalized restoration of SOX10-related activity.	Proof-of-concept in demyelination models.	Disease-context transferability and off-target biology remain concerns.	[24]

7. Conclusion

SOX10 integrates embryonic signaling, enhancer logic, lineage competence, and tissue maturation across neural crest-derived populations [1–4,8,15,9-14,20]. Waardenburg syndrome, Hirschsprung disease, auditory dysfunction, and glial vulnerability are different outputs of one developmental control problem [6,20,7,16,8]. Precision medicine will depend on lineage-resolved, dosage-aware intervention.

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