Purpose of review
Sensory hair cells (HCs) of the inner ear are responsible for our ability to hear and balance. Loss of these cells results in hearing loss. Stem cell replacement and in situ regeneration have the potential to replace lost HCs. Newly discovered contributions of transcription factor regulatory networks and epigenetic mechanisms in regulating HC differentiation and regeneration are placed into context of the literature.

Recent findings
A wealth of new data has helped to define cochlear sensory progenitors in their developmental trajectories. This includes transcription factor networks, epigenetic manipulations, and cochlear HC subtype specification.

Summary
Understanding how sensory progenitors differ and how HC subtypes arise will substantially inform efforts in hearing restoration.

Keywords
epigenetic modifications, feedforward loops, progenitor cells, sensory progenitors

INTRODUCTION
Encased in a bony labyrinth, the cochlea enables us to discriminate and hear complex sounds. The cells responsible for our initial percept of sound are called sensory hair cells (HCs). Ototoxic damage from loud noise exposure, genetic mutations, and aging drive HC death. As the mature cochlea cannot regenerate, HC death causes hearing loss. Acquired hearing loss imposes a significant socioeconomic burden [1,2]. Current treatments for individuals with hearing loss are limited. Hearing aids or cochlear implants augment residual sensory function and improve patient quality of life, but fall short of providing permanent cures that might be achievable through regenerative efforts. Strategies to regenerate lost HCs are essential for treating a wide spectrum of hearing loss.

To understand cochlear HC regeneration, it is necessary to describe its differentiation in vivo. Sensory progenitors localize to a patch of cells in the primordial mouse cochlea, called the prosensory zone [3]. Sequential, spatially localized signals are required to specify, maintain, and differentiate sensory progenitors. Early NOTCH signaling may specify the proliferating sensory progenitors, coinciding with SOX2 expression at ~E12.5 [4,5] but see [6] for a different interpretation. Sensory progenitors further require FGFR1 [7] and GSK3β kinase signaling to maintain the prosensory zone prior to cell cycle exit [8]. Laterally, GSK3β signaling maintains BMP4 expression [9], which is required for sensory precursors to upregulate CDKN1B and withdraw from the cell cycle at E13.5 [10].

After lineage specification and cell cycle withdrawal, prosensory cells transition to a second state,
where GSK3β or NOTCH inhibition now promotes HC differentiation [8,11]. In the second state, the sensory progenitors respond to local variance in signaling to become specified as HCs and supporting cells (SCs, Fig. 1). Differentiation begins in the base with the induction of the transcription factor ATOH1 [12]. After cell-type specification, sensory cells enter a third state, where signals including endogenous NOTCH promote continued maturation [13]. These signals also regulate endogenous lineage conversion, which may further refine the mosaic pattern of cells characteristic of the organ of Corti.

Differentiation of cochlear progenitors to HCs arises from a nested series of incoherent and coherent feedforward loops and positive and negative feedback loops. These loops are carried out by transcription factor networks. In incoherent feedforward loops, an inducer drives the expression of both an outcome product and antagonists for that product. Modeling this gene logic in differentiation has shown that it translates gradients of inducing activity into uniform levels of gene expression outcomes [14]. In contrast, coherent feedforward loops have inducers that promote both the outcome and intermediate products to positively reinforce the outcome product’s activity. This logic amplifies and sustains the gene network. In feedback loops, outcome products positively or negatively impact the activity of themselves or their inducers.

Figure 2 shows a simplified network of factors that promote or repress the expression of ATOH1, with positive regulators and negative regulators in different shades. SOX2 binds to the promoter of Atoh1 to induce its expression [15]. ATOH1 binds to its own enhancer to up-regulate its own expression in a positive feedback loop [16], making this action a key transition point in HC differentiation [17]. Autoregulation by ATOH1 initially requires SOX2 protein [18]; however, higher or sustained levels of SOX2 protein have an opposing effect [15]. Moreover, SOX2 concomitantly drives the expression of ATOH1 antagonists, including Id and HES/HEY family members. Thus, SOX2, ATOH1 antagonists, and ATOH1 form an incoherent feedforward loop as described [18]. ATOH1 reduces SOX2 activity with negative feedback. This occurs directly by ATOH1 binding to SOX2’s promoter [18], and indirectly through ATOH1’s regulation of NOTCH signaling.

In contrast, SIX1/EYA1 form a coherent feedforward loop with ATOH1, with mutual targets as the outcome products. Evidence for this role comes from a new study correlating SIX1 binding sites with active chromatin [19**]. With EYA1, SIX1 binds directly to ATOH1’s promoter independently of SOX2 to promote Atoh1 transcription. Although SOX2 and EYA1 protein are both present in the sensory zone prior to HC differentiation, SIX1 protein expression coincides with ATOH1 protein as the first inner hair cells (IHCs) differentiate at E14.5 [20]. SIX1/EYA1 cooperate with ATOH1 to induce downstream targets, including other HC transcription factors such as POU4F3 and GFI1 [20] and proteins required for hearing [19**]. Although still incomplete, these findings have substantially informed studies of HC regeneration. Many studies use overexpression of ATOH1 and its co-factors to drive HC differentiation in regeneration studies [21].
Accumulating evidence suggests that in addition to changes in transcription factor profiles, alterations in the epigenetic landscape are crucial for efficient regeneration for both directed differentiation and lineage conversion. Simplistically, chromatin accessibility can pose a barrier for changes in cell identity. All nuclear DNA in eukaryotes is organized as chromatin, where DNA is wrapped around histone octamers consisting of H2A, H2B, H3, H4 histone subunits and variants [22]. Studies on post-translational histone modifications have led to the concept of the ‘histone code’, which defines the local functional potential of a chromatin region [23]. Compaction of DNA into chromatin is a significant barrier for macromolecular complex binding, which must be actively overcome to make the chromatin accessible for the initiation of transcription. Changes in chromatin can activate or silence transcription by controlling promoter accessibility and regulating transcription factor binding [22].

**STEM CELL REPLACEMENT AND IN SITU REGENERATION USING OTIC PROGENITORS**

A goal of cochlear regeneration is to repopulate lost HCs in human adults where there is little to no regenerative capacity. Cell replacement through directed differentiation of transplanted otic progenitors and through in situ regeneration via lineage conversion have been proposed to replace damaged or lost HCs. Both processes rely on progenitors that are competent to become HCs. Although the progenitor state in each paradigm may be different, they likely possess a common epigenetic signature required for HC competency.

Although there are major hurdles for engrafting stem cell into cochleae for replacement therapies [24], some of these obstacles have been addressed. Human otic progenitor cells generated from induced pluripotent stem cells (iPSCs) and differentiated in vitro can express known otic progenitor markers [25]. When transplanted into an adult guinea pig model of ototoxicity, such cells can engraft in nonsensory regions and survive up to

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**FIGURE 2.** Transcription factor networks surrounding ATOH1. Positive regulators (bottom half) and negative regulators (upper half) are shown. Inductive activities are shown with arrows; repressive activities are indicated by an ending bullet point. Thick black lines indicate a direct binding activity on DNA; thinner, lighter lines indicate a genetic dependence, and dotted lines indicate known indirect interactions.
4 weeks posttransplantation. Some engrafted otic progenitor cells resided within the cochlear sensory epithelium and displayed markers of early sensory differentiation [26]. Thus, directed differentiation of iPSCs into an otic progenitor state allows for cells to be engrafted in the cochlea and differentiate into HC-like cells.

In addition to iPSCs, Lgr5+ SCs from newborn and adult murine cochlea can act as otic progenitors. When cultured in a single-cell suspension, purified Lgr5+ SCs form neurospheres and self-renew. Lgr5+ cells can differentiate into HCs, demonstrating cochlear progenitor capacity [27]. Although promising, this capacity may be restricted to fetal stages in humans. A study using adult human temporal bones found that similar progenitor cells could only be isolated from vestibular maculae and not from cochlea [28].

For in situ regeneration, use of SCs that reside next to lost HCs has been proposed. When the dipheria toxin receptor is engineered for HC expression in mice, the injection of dipheria toxin A allows for selective HC ablation. After HC ablation at birth, spontaneous regeneration of HCs occurs. Fate-mapping shows quiescent SCs proliferate and acquire a HC fate after damage. The findings demonstrate that the immature SCs in the mouse cochlea can spontaneously regenerate lost HCs in vivo. Regeneration does not occur when HC ablation was induced at one week of age [29]. As cells in the cochlea mature, epigenetic changes may contribute to the inability for HCs to regenerate [30]. It is likely that cellular plasticity is lost as epigenetic marks for maturing cells are established.

The age-related decline in cellular plasticity in SCs can be overcome by initiating proliferation. Transient expression of MYC and NOTCH1 enables adult SCs to respond to the ATOH1 mediated lineage conversion of SCs into HC-like cells. The study suggests that co-activation of MYC and NOTCH1 is sufficient to reprogram fully mature SCs to proliferate and regenerate HC-like cells in adult mammalian auditory organs [31]. In S-phase of the cell cycle, nucleosomes and the associated chromatin architecture disassemble in front of replication forks and then reassemble with newly synthesized DNA and histones [32]. Nucleosome spacing and accessibility are disrupted and have to be re-established for daughter cells to retain the same epigenetic state as the mother cell [33]. Thus, DNA replication could enable more accessible chromatin regions, allowing ATOH1 to activate target genes. This represents a window of opportunity for cellular plasticity in nascent daughter cells, which may become reprogrammed as cochlear progenitors.

**EPIGENETIC CHANGES THAT PROMOTE HAIR CELL REGENERATION**

Hereditary hearing loss or deafness has been associated with mutations in genes that code for proteins that regulate histone modification, DNA methylation, and chromatin remodeling [34]. Although the processes of directed differentiation and lineage conversion may differ, insight into chromatin alterations during development informs of specific molecular epigenetic processes that could be employed for regeneration. Evidence for an epigenetic barrier that prevents cellular plasticity includes studies showing that adding DNMT inhibitors, 5-Azacytidine and HDAC inhibitors such as trichostatin and valproic acid or expression of chromatin remodelers such as BRG1 can allow for reprogramming [35].

**Histone methyltransferase and acetyltransferase**

The transcription factor ATOH1 is often used as a prototypic target gene to promote HC regeneration. However, cochlear prosensory cells and differentiated SCs inhibit Atoh1 expression. At the Atoh1 locus of these cell types, bivalent marks containing both repressive (H3K27me3) and active (H3K4me3) epigenetic marks are present at regulatory sequences, indicating that Atoh1 is poised for expression. In differentiated HCs, bivalent marks were infrequent. H3K9ac, a mark associated with actively transcribed genes, was present instead [36]. Inhibition of histone acetyltransferase activity reduced H3K9ac at the Atoh1 locus, preventing Atoh1 induction. In contrast, repression of Atoh1 expression in maturing HCs resulted in H3K9 deacetylation and an increased frequency of H3K9me3, a mark associated with silenced chromatin [37]. These results point to a central role for histone acetyltransferases in controlling cis-regulatory elements of Atoh1 locus [38], and manipulating this process can be employed to facilitate regeneration.

**DNA methyltransferases**

DNA methyltransferase 1 (DNMT1) is an enzyme responsible for the deposition and maintenance of cytosine methylation in CpG dinucleotides in vertebrate somatic cells. In differentiated cells, methylation in CpG islands at transcription start sites prevents transcription. By inhibiting methyltransferases, one could decrease methylation at promoters and allow transcription of genes that are normally repressed.
To achieve gene silencing, DNA methylated by DNMT1 recruits the methyl-CpG-binding protein MECP2. In turn, MECP2 recruits histone deacetylase 1 (HDAC1) to these regions to modify histones. Histone deacetylation prevents transcription [39]. The introduction of 5-azacytidine to inhibit methyltransferase in the inner ear allows for generation of nascent HCs in adult animals treated with aminoglycosides. Lineage tracing of SOX2+ SCs shows that these nascent HCs arise from SCs 5–7 days after treatment [40]. The study suggests that global inhibition of DNA methylation allows expression of HC specifying genes in SCs to facilitate lineage conversion in vivo.

**Chromatin remodeling**

Perhaps the most potent mechanism of epigenetic manipulation is the use of ATP-dependent chromatin remodeling enzymes that can re-position, evict, or alter the composition of nucleosomes. Indeed, several chromatin remodeling enzymes reposition histone octomers and play an integral role in regulating nucleosome distribution. Nucleosome placement confers epigenetic information including chromatin accessibility.

Genetic variations in this class of chromatin remodeling proteins, including CHD7, cause syndromic hearing loss. The chromodomain of CHD7 binds to methylated histones to allow association with chromatin. In vitro nucleosome assays show that CHD7 increases chromatin accessibility [41] and associates with enhancers and promoters to regulate gene expression [42,43]. A recent study using a pan-otic deletion of CHD7 found that this manipulation leads to additional outer HCs (OHCs) [44**]. This suggests that CHD7 alters chromatin accessibility of key genes during development to regulate HC numbers.

**BEYOND ATOH1: HOW OUTER HAIR CELLS BECOME DIFFERENT FROM IHCs**

Critical to any regeneration strategy is the ability to differentiate the correct ratio of IHCs and OHCs. Current inner ear organoid models have successfully generated HC-like cells in vitro with appropriate electrophysiological characteristics [45,46]. However, the generation of cochlear HCs with expression profiles matching IHCs and OHCs remains elusive [47]. A better understanding of the temporal, spatial, and concentration-dependent factors that regulate OHC differentiation may be key to addressing this problem. A number of excellent new studies are helping to improve our understanding of cochlear HC sub-type specification.

Some progenitors for OHCs and lateral SCs are differentially specified from medial progenitors at E12.5 in the mouse, as shown by fate-mapping studies [48] and new single-cell sequencing studies [49**]. After cell cycle withdrawal, lateral progenitors express FGFR1 and Prox1 [49**] and subsequently FGFR3 [50]. In other systems, PROX1 directly binds FGFR3’s promoter, driving its expression [51]. Lateral progenitors express FGF20, a candidate ligand for FGFR1-dependent differentiation of OHCs. This specification event is prior to ATOH1 induction and NOTCH-dependent lateral inhibition [52].

Lateral organ of Corti cells remains distinct from medial cells throughout development and into adulthood. Recent studies combining single-cell chromatin accessibility profiles with single-cell sequencing from neonatal mouse cochleae have identified 23 transcriptional activators and repressors regulating HC differentiation, with HIVEP2 specific to IHCs and insulinoma-associated 1 (INSM1) specific to OHCs [53**]. INSM1 is critical for blocking the expression of IHC genes in OHCs [54]. RXF3, Pou3f2, and HELIOS are subsequent transcriptional activators that promote actin binding protein expression, neurotrophins, and electromotility in OHCs [55]. Notably, adult cochlear SCs form transcriptionally distinct populations of medial and lateral cells [56**]. These studies have found that lateral adult SCs maintain some transcriptional commonality with LGR5+ neonatal SCs [56**,57], suggesting that they may be manipulated to regenerate OHCs.

**CONCLUSION**

Neonatal and even mature SCs can be genetically manipulated to become otic progenitors and coaxed into differentiating HCs. However, spontaneous lineage conversion has not been observed after damage in the mature mammalian cochlea. Changes in the epigenome are likely a contributing factor that inhibits lineage conversion. Recent studies on sensory specification, HC differentiation and subtype specification, and induced otic progenitor populations bring us closer to the day when cochlear HC regeneration may become a reality.

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Conflicts of interest

There are no conflicts of interest.

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