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Abstract:

The inner ear contains specialized sensory epithelia that detect head movements, gravity and sound. Hearing loss and imbalance are primarily caused by degeneration of the mechanosensitive hair cells in sensory epithelia or the sensory neurons that connect the inner ear to the brain. The controlled derivation of inner ear sensory epithelia and neurons from pluripotent stem cells will be essential for generating in vitro models of inner ear disorders or developing cell-based

therapies. Despite some recent success in deriving hair cells from mouse embryonic stem (ES) cells, it is currently unclear how to derive inner ear sensory cells in a fully defined and reproducible manner. Progress has likely been hindered by what is known about induction of the nonneural and preplacodal ectoderm, two critical precursors during inner ear development. The studies presented here report the step-wise differentiation of inner ear sensory epithelia from mouse ES cells in three-dimensional culture. We show that nonneural, preplacodal and pre-otic epithelia can be generated from ES cell aggregates by precise temporal control of BMP, TGFβ and FGF signaling, mimicking in vivo development. Later, in a self-guided process, vesicles containing supporting cells emerge from the presumptive otic epithelium and give rise to hair cells with stereocilia bundles and kinocilium. Remarkably, the vesicles developed into large cysts with sensory epithelia reminiscent of vestibular sense organs (i.e. the utricle, saccule and crista), which sense head movements and gravity in the animal. We have designated these stem cell-derived structures inner ear organoids. In addition, we discovered that sensory-like neurons develop alongside the organoids and form putative synapses with hair cells in a similar fashion to the hair cell-to-neuron circuit that forms in the developing embryo. Our data thus establish a novel in vitro model of inner ear organogenesis that can be used to gain deeper insight into inner ear development and disorder.

Description:

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