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Opposing Actions of Cell-Intrinsic Factors and Secreted Signals Regulate Neurogenesis in Olfactory Epithelium

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Stem Cells in Sensory Epithelium Development and Regeneration

Development and Regeneration in the Mammalian Inner Ear: Cell Cycle Control and Differentiation of Sensory Progenitors

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Sensory hair cell loss is the leading cause of deafness in humans. The mammalian cochlea cannot regenerate its complement of sensory hair cells, and thus at present, the only treatment for deafness due to sensory hair cell loss is the use of prosthetics such as hearing aids and cochlear implants. In contrast, in non-mammalian vertebrates such as birds, hair cell regeneration occurs following the death of hair cells and leads to the restoration of hearing. Regeneration in birds is successful because supporting cells that surround the hair cells begin to divide when hair cells are lost and are able to subsequently differentiate into new hair cells. Although these cells exist in mammals, they do not normally divide or transdifferentiate when hair cells are lost, and so regeneration does not occur. To understand the failure of mammalian cochlear hair cell regeneration, we have been studying the molecular mechanisms that underlie cell division control and hair cell differentiation, both during embryogenesis and in the postnatal mouse. In this presentation, I will discuss the molecular basis for the timing of cell cycle exit in the embryo, and how this is coordinated with differentiation to produce the correct number of hair cell and supporting cell precursors to build a functional organ of Corti. I will also discuss the role of the Cip/Kip cell cycle inhibitors and Notch signaling in the control of stability of the differentiated state of early postnatal supporting cells. Finally, I will present data indicating that some early postnatal mammalian supporting cells retain a latent capacity to divide and transdifferentiate into sensory hair cells. Together, these observations make supporting cells important therapeutic targets for continued efforts to induce hair cell regeneration.

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Fate Mapping Mammalian Taste Bud Progenitors: New Insights, Challenges and Beyond

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Despite some neuronal characteristics, taste receptor cells arise from the local epithelium unlike other sensory receptors, which derive from neurogenic ectoderm. Like other epithelial appendages, taste organs form as epithelial placodes, followed by intervention of mesenchymal core to form taste papillae. Taste buds differentiate in the papillary epithelium around birth. However, evidence for a lineage relationship between the embryonic placodes and functional taste buds is primarily indirect. Likewise, while mesenchyme plays a role in the morphogenesis of most epithelial appendages, its function in mammalian taste bud and papilla development is unclear. To understand the developmental relationship of taste buds and papillae, and the interplay between papillary epithelium and mesenchyme, we used a fate mapping approach to indelibly label either embryonic taste placodes, or the cranial neural crest-derived mesenchyme and followed the postnatal fates of these cell populations. With the inducible ShhCreERT2 mouse line crossed to R26R reporter line, we demonstrate embryonic Shh-expressing taste placodes are taste bud progenitors, which give rise to the differentiated taste cells. In contrast, with Wnt1-Cre mediated recombination, we show that cranial neural crest-derived mesenchyme contributes only to the mesenchymal core of taste papillae and not to taste buds or papillary epithelium. Recently, we have shown that these taste bud progenitors are specified by Wnt8b-catenin, a key pathway in the induction of other epithelial appendages. We are now exploring the role of WNT signaling with respect to its function within the taste bud progenitor population and its impact on papillary morphogenesis.

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Wnt5a in Tongue and Taste Papilla Development

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Wnt10b has a critical role in formation of fungiform papillae, via canonical Wnt signaling. In a gene array experiment we found that Wnt5a, which can signal in either the canonical or non-canonical pathway, was increased 8 fold in anterior tongue of rat embryo organ cultures, compared to posterior tongue. In Western blots, Wnt5a was expressed in tongues from embryonic (E) day 13 through 16. Immunoreactions in E15 tongue demonstrated Wnt5a in epithelium and mesenchyme. To learn if Wnt5a has a role in development of papillae, we compared tongues of E15.5 - 17.5, Wnt5a –/– mutant mice with those of wild type littermates. Length of oral tongue in Wnt5a null mouse was reduced to 60% of wild type length. Portions of the tongue that were anterior, or posterior, to the anterior-most border of the intermolar eminence were reduced by similar proportions. However, pharyngeal tongue in null mice was reduced only to 25% of wild-type. Whereas length of oral tongue was severely compromised in null mice, width was similar to that in wild type. Thus overall, area of the anterior tongue was substantially reduced and shape was radically altered. In the face of a much truncated anterior tongue area, numbers of fungiform papillae were not different on mutant tongues relative to wild type. This separates genetic programs for papilla number from those for tongue shape and size. The single circumvallate papilla on posterior tongue also was sustained, but with topographical shrinkage and shape alteration in Wnt5a mutant tongues. Results demonstrate a role for Wnt5a in tongue and circumvallate papilla size and shape, in distinction to roles for Wnt10b in establishing fungiform papilla number.

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Opposing Actions of Cell-Intrinsic Factors and Secreted Signals Regulate Neurogenesis in Olfactory Epithelium

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In mouse olfactory epithelium (OE), growth and differentiation factor 11 (GDF11), an activin-like TGF-β expressed by olfactory receptor neurons (ORNs) and late-stage neuronal progenitors, acts to inhibit both proliferation and neuronal differentiation of neuronal progenitor cells. FoxG1, which encodes a forkhead-box transcription factor known to be required for OE development, is co-expressed with Gdf11 in much of developing OE; and FoxG1 is known to interact with Smad transcription complexes to inhibit expression of TGF-β target genes. Together, these observations raise the possibility that
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**Onset of Odorant Receptor Expression**

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Olfactory sensory neurons (OSNs) express 1 of ~1,000 odorant receptors (ORs). OSNs projecting axons to the same glomeruli express the same OR protein, although they are distributed within restricted regions of the olfactory epithelium (OE). As the OSN axons navigate from the OE to the olfactory bulb (OB), they reorganize and project to specific glomeruli based on OR expression, among other cues. This expression pattern is not achieved simply via retrograde signals from the OB after synapse formation because: 1) ORs are expressed during embryonic development prior to synapse formation; and 2) ORs are also expressed in mice lacking OBs. ORs are expressed prior to synapse formation, but it remains to be established when ORs are first expressed during development. The aims of this work were 3-fold: 1) study onset of OR expression for a subset of ORs; 2) determine if there is a preferential zonal or chromosomal OR expression choice during embryogenesis; and 3) perform a quantitative analysis of specific OR expressing OSNs. We found that the onset of OR gene expression is asynchronous. For example MOR244-1 is first expressed at very early stages of olfactory development, while MOR245-3 only appears late in embryogenesis. Interestingly, OR onset does not seem to be stochastic during development; i.e. ORs on some chromosomes appeared overrepresented early in development. Moreover, expression of ORs from the same region/zone have differential onsets of expression, and the profile of numbers of cells expressing a given OR is not uniform, but varies by OR; some ORs had profiles that increased with age while some had a more transient expression. Our results provide compelling evidence that OR choice could be an important determinant of glomerular targeting during embryogenesis.

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**Transcriptional Control of Epidermal Morphogenesis**

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The epidermis is the primary barrier that protects the body from dehydration, mechanical trauma, and microbial insults. This barrier function is established during embryogenesis through a tightly controlled stratification program. One gene that is critical for controlling epidermal morphogenesis is p63, a transcription factor that can be expressed as isoforms that contain (TA) or lack (AN) a transactivation domain. Of these, ΔNp63 isoforms are the predominantly expressed p63 isoforms in late embryonic and postnatal epidermis. To determine the role of ΔNp63 proteins, we generated an epidermal-specific inducible ΔNp63 knockdown mouse model. We found that downregulating ΔNp63 expression in postnatal epidermis caused severe epidermal defects, including aberrant keratinocyte differentiation and impaired basement membrane formation, culminating in the development of severe skin erosions. Interestingly, these lesions were indistinguishable from lesions that develop in patients with AEC, an ectodermal dysplasia caused by mutations in ΔNp63a. Follow-up studies demonstrated that, during epidermal morphogenesis, ΔNp63a initially induces expression of a keratinocyte-produced extracellular matrix protein, Fras1, which is required for maintaining the integrity of the epidermal-dermal interface at the basement membrane. Subsequently, ΔNp63a initiates epidermal terminal differentiation by inducing IKKα, a regulator of epidermal, skeletal, and craniofacial morphogenesis. Together, our data provide novel insights into the role of ΔNp63a in epidermal morphogenesis and homeostasis, and may contribute to our understanding of the pathogenic mechanisms underlying disorders caused by p63 mutations.

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