Archives Italiennes de Biologie, 148: 107-118, 2010.

Taste bud regeneration and the search for taste progenitor cells

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ABSTRACT

While the taste periphery has been studied for over a century, we are only beginning to understand how this important sensory system is maintained throughout adult life. With the advent of molecular genetics in rodent models, and the upswing in translational approaches that impact human patients, we expect the field will make significant advances in the near future.

Key words

Molecular genetics • Mouse • Sonic hedgehog (Shh) • Wnt/β(beta)-catenin • Gustatory system

Introduction

Taste is a primary sense of all vertebrates, reliably conveying important chemical information from the oral cavity to the brain to regulate ingestion. For most animals, sweet, moderately salty or certain amino acid stimuli trigger appetitive behavior, while bitter or sour substances are typically aversive (Roper, 2007). The ability of animals to make this distinction between nutritional, versus potentially lethal, or fermented or unripe food items, respectively, may mean the difference between survival and death (see Barlow, 1999).

In sum, the taste system consists of several anatomical and functional components, including a distributed array of taste buds within the oral and pharyngeal cavities (but see Herrick, 1903; Hara, 1994; Northcutt, 2004). Taste buds are multicellular end organs of roughly 50-100 fusiform cells, which transduce sapid stimuli into electrochemical signals. These cells comprise a heterogeneous population including taste responsive cells, the majority of which serve one particular taste modality, such as sweet, sour, bitter, umami (Japanese for "deliciousness"; glutamate taste) or salty (Chandrashekar et al., 2006; Roper, 2007; Tomchik et al., 2007; Yoshida et al., 2009). These sensory cells communicate via neurochemical signals with afferent nerve fibers of gustatory sensory neurons. These sensory neurons are pseudobipolar, with cell bodies located in one of several cranial ganglia (VII, IX or X); their distal neurites extend to peripheral taste buds, and their proximal neurites project centrally, to specific regions of the brainstem. While both central and ganglionic neurons are relatively static, cells within taste buds continually turnover throughout adulthood such that roughly 10% of cells are new to each bud each day (Beidler and Smallman, 1965; Farbman, 1980). Despite this persistent regeneration of taste sensory cells, the percept of taste is relatively constant over time; a salty or sweet item identified at one time in the past, is consistently salty or sweet in the present and likely in the future. How is this constancy attained at a cellular level?

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Like neurons, taste receptor cells are electrochemically excitable and release neurotransmitter onto afferent nerve fibers upon excitation (Roper, 1989). However, unlike neurons which arise embryonically from neurogenic ectoderm, the origin of these chemosensory cells is epithelial (Barlow and Northcutt, 1995; Stone et al., 1995). Thus continual regeneration of taste cells may be driven by cellular and molecular mechanisms which reflect their function (neural), their origin (epithelial), or some combination thereof.

In this brief review, we have chosen to highlight recent findings pertaining to taste cell biology and renewal in rodent models, primarily in mice. In particular, we focus on exciting new data addressing both molecular and cellular mechanisms that regulate this key sensory system. While we do provide a brief overview of pertinent background here, we also refer our readers to several other excellent reviews, which thoroughly address other important aspects of taste biology including transduction (Breslin and Huang, 2006; Roper, 2007; Breslin and Spector, 2008), development (Krimm, 2007), and genetics (Boughter and Bachmanov, 2007). Recently, one of us published a systematic review of taste cell lineage and renewal (Miura et al., 2006), thus our current review serves to update several topics covered in this last publication.

The cell biology of taste bud regeneration

Within the oral cavity of mice and rats, taste buds are located within specialized papillae on the tongue, as well as in defined epithelial domains of the palate, nasoincisor duct, pharynx and larynx. Researchers have focused predominantly on lingual taste buds in the fungiform papillae (each with a single taste bud) arrayed on the anterior two thirds of the tongue, and on the larger posterior papillae, the single midline circumvallate and bilateral foliates (each housing several hundred buds) (Kinnamon, 1987). In addition, rodents have a large collection of taste buds embedded in the epithelium of the soft palate, which has also been the subject of numerous studies (e.g. Mistretta, 1972; Harada et al., 2000; El-Sharaby et al., 2001; Zhang et al., 2008). In mice and rats, the cellular makeup of taste buds in each of these taste fields is roughly comparable and consists of: type I cells, which are believed to function as support cells (Lawton et al., 2000; Finger et al., 2005; Bartel et al., 2006; Dvoryanchikov et al., 2009); sweet, bitter and umami (glutamate taste) detecting type II receptor cells (Chandrashekar et al., 2000; Nelson et al., 2001; Nelson et al., 2002; Zhang et al., 2003; Zhao et al., 2003); and sour and salt sensing type III cells (Richter et al., 2003; Huang et al., 2006; Chandrashekar et al., 2010; Nguyen and Barlow, Submitted). However, regional and papilla-specific differences do exist for type II cells in terms of the specific taste transduction proteins they express (Kim et al., 2003; Miura et al., 2007; Shindo et al., 2008; Tizzano et al., 2008). Type I cells are assumed to be the most numerous, representing approximately 50% of cells per bud, while type II and III cells are less common, contributing 15-20% each (Ma et al., 2007). How are these cells generated?

A significant number of studies have reported that cells within taste buds are postmitotic, i.e., they do not express markers of cycling cells such as Ki-67, PCNA, and phosphohistone3A (Hirota et al., 2001; Nguyen and Barlow, Submitted) but do express proteins which inhibit cell cycle progression, such as p27Kip1 and p21Cip1 (Hirota et al., 2001) (but see Toyoshima and Tandler, 1986). Moreover, birthdating studies employing thymidine or its analog, BrdU, have revealed that epithelial cells immediately adjacent to taste buds are in S phase when animals are examined within 1-6 hours of nucleotide labeling, while no labeled cells are encountered within taste buds at this point. Within 12-24 hrs of BrdU or thymidine injection, however, post-mitotic labeled cells are evident within taste buds, and by 48-72 hours, these immature cells differentiate, as evidenced by their expression of specific taste cell type immunomarkers (Beidler and Smallman, 1965; Farbman, 1980; Delay et al., 1986; Cho et al., 1998; Yee et al., 2003; Miura et al., 2006; Asano-Miyoshi et al., 2008).

By contrast, in taste papillae large numbers of perigemmal (adjacent to taste buds proper) and basal epithelial cells are mitotically active (Fig. 1; Beidler and Smallman, 1965; Delay et al., 1986; Hirota et al., 2001; Hendricks et al., 2004; Miura et al., 2004; Nguyen and Barlow, Submitted). These cells are likely the proliferative pool from which immature taste cells are generated via a process hypothesized

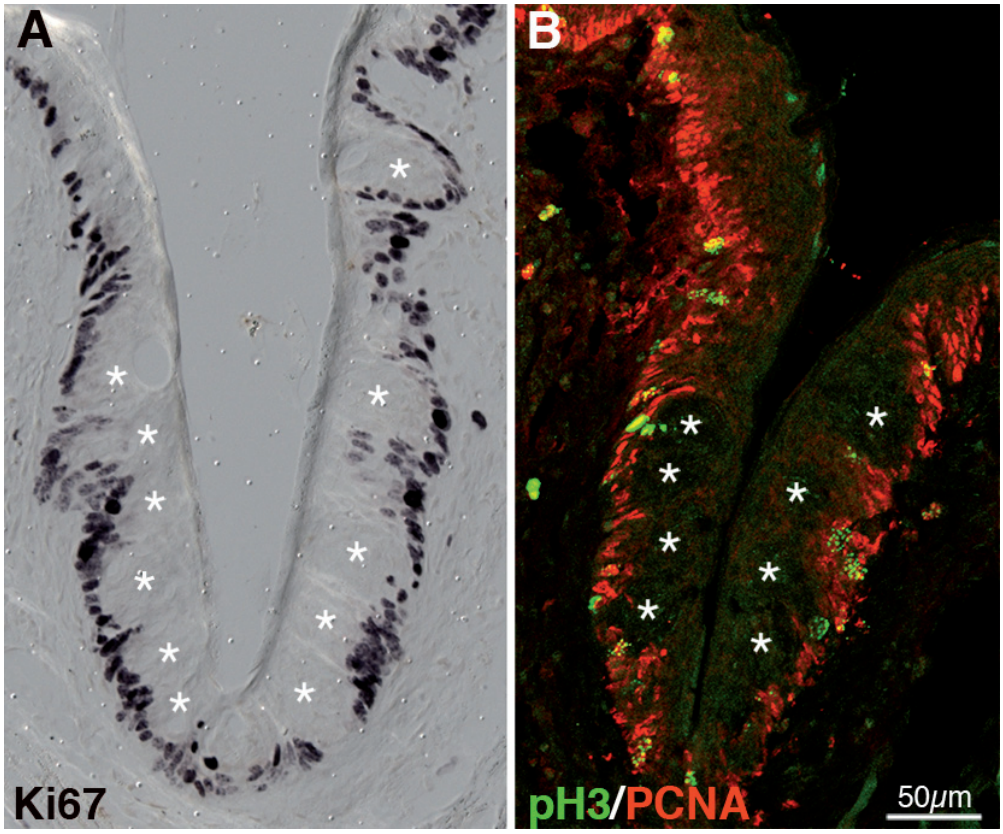

Fig. 1. - Immunostaining with a variety of cell cycle markers reveals that cells within taste buds (white asterisks) of the circumvallate taste papilla are postmitotic. In A and B, only one cleft of the circumvallate papilla is shown in sections taken transverse to the tongue. Taste buds are arrayed in the epithelium lining the cleft, with their apices directed toward the cleft lumen. A. Ki67 marks cells in all phases of the cell cycle, including G1, S, G2 and M, but not resting cells in G0 (Schwarting et al., 1986). Note that basal and perigemmal epithelial cells are immunostained, while intragemmal cells are not. B. PCNA (red) is expressed by cells in all phases of the cell cycle except G1 (Celis et al., 1986), while phosphoHistone3 (pH3; green) is expressed only during M phase (Norbury and Nurse, 1992). Again, immunostained cells are located outside of taste buds (white asterisks), defining the location of the proliferating cells within the circumvallate papilla. The dorsal surface of the tongue is up in both panels. Images courtesy of Ha M. Nguyen.

to resemble that of general epidermis, i.e., a small number of taste bud stem cells divide infrequently and asymmetrically to give rise to a transit amplifying (TA) daughter, which in turn divides symmetrically and these cells either divide again or enter taste buds as postmitotic, immature taste cells. Based on the distribution of labeled cells in an X-inactivation reporter mouse line, Tom Finger and colleagues have estimated that each mouse taste bud is populated by between 7 and 13 putative stem cells (Stone et al., 2002). However, to date, molecular markers that allow discrimination of taste bud stem from TA cells have remained elusive, a situation very comparable to the stem and TA cells of the interfollicular epidermis (Watt et al., 2006; Watt and Jensen, 2009).

Perigemmal cells of taste buds, but not taste cells themselves (but see Asano-Miyoshi et al., 2008), express cytokeratins 5 and 14 (K5 and K14) (Lee et al., 2006; Asano-Miyoshi et al., 2008; Okubo et al., 2009), which are also expressed by the regenerative cell population of the skin, the basal keratinocytes of the general epidermis (Bragulla and Homberger, 2009). Most recently, Okubo and colleagues have used tissue specific, inducible molecular genetic tools to map the progeny of K14-expressing basal keratinocytes located in taste epithelium (Okubo et al., 2009). In short, indelible lacZ reporter gene expression was induced by tamoxifen treatment of mice carrying: 1) one allele with the human K14 promoter (hK14) driving a fusion protein of Cre recombinase and the tamoxifen-sensitive form of an estrogen receptor (Vasioukhin et al., 1999); and

2) a second allele where the constitutive promoter of the R26 locus driving lacZ is downstream of a flox-stop-flox cassette (Soriano, 1999). Results from these studies are tantalizing, but inconclusive. Certainly, hK14-expressing basal keratinocytes give rise to cells within taste buds, as well as to papillary epithelium and general lingual epithelium. In some instances, potentially clonal clusters of labeled cells comprised both taste bud and papilla cells, suggesting that K14+ basal cells are multipotent. However, to resolve this issue, one needs to examine the initially labeled cell(s), and follow their descendents more closely, perhaps by titrating downward the tamoxifen dose to label only a very few cells per animal.

Basal keratinocytes of the lingual epithelium and taste papillae also express the transcription factors Trp63 at high levels, and Sox2 at low levels (Okubo et al., 2009). The expression characteristics of K14+Trp63+K5+Sox2+ cells have been thus suggested to define the taste bud progenitor pool. In an attempt to assay the differentiative potential of this cell population, this group obtained and cultured a population of highly fluorescent cells from the lingual epithelium of mice carrying an allele where the human cytokeratin 5 promoter drives GFP (Luo et al., 2009). This approach yielded epithelial stem cells, which could give rise to differentiated epithelium, but did not appear to produce taste buds and their resident receptor cells.

Molecular and cellular mechanisms of taste cell genesis

Additional new data on genesis of taste cells comes from studies of embryonic development of the taste epithelium. While taste cells differentiate around birth both in rats and mice, the first indication that these structures have been specified occurs at mid-gestation. In mice, the tongue forms from bilaterally paired lingual swellings, which fuse at the midline by embryonic day (E) 11.0-11.25. By E12.5, a series of focal epithelial thickenings, or placodes, form in 2 bilateral rows, presaging the location of fungiform papillae in adults (Fig. 2). Importantly, these placodal cells express both the mRNA and protein for Sonic Hedgehog (Shh) at this early developmental stage. While taste placodes have been assumed to represent papillary precursors (Mistretta and Liu, 2006), the fate of these Shh-expressing cells had not been determined. Using a similar inducible molecular genetic schema to Okubo and colleagues, we used mouse embryos harboring an allele where the native Shh coding region was replaced by the Cre-ERtam fusion protein (Harfe et al., 2004) and the Rosa LacZ reporter allele to map the fate of Shh-expressing taste placodes. By treating pregnant females with tamoxifen precisely when Shh is focally expressed in the taste placodes of the embryos, we found that these cells were progenitors for differentiated taste cells in postnatal animals, but did not contribute to taste papilla epithelium (Thirumangalathu and Barlow, 2009; Thirumangalathu et al., 2009). Moreover, it was also shown that at least type I and II taste cells descended directly from Shh-expressing taste placode cells, indelibly marked between E12.5 and E14.5. An additional hypothesis addressed by our study was that the embryonic Shh-expressing taste progenitors would persist in adult mice as taste bud stem cells. However, this was not the case; rather, taste bud cells descendent from Shh-expressing placodes were gradually lost postnatally, and were completely absent 4 months after birth. Given these findings, we have proposed that the Shh-expressing placodal cells function as a signaling center in embryos and young postnatal animals, and that additional progenitor cells are recruited in adult mice to take over the required function of continual cell replenishment of mature taste buds, much like the scenario demonstrated for murine hair follicles (Nowak et al., 2008). The recruitment of additional progenitor cells expressing Shh is assumed to continue in the basal region of taste buds throughout life, as described later. Alternatively, Shh-expressing taste bud stem cells may be set aside earlier or later in embryogenesis, such that fate mapping studies performed at earlier or later time points will reveal this stem population. Studies are underway to test these different ideas.

Shh is also expressed in adult taste buds of mice. In addition to the fusiform taste cell types I, II and III, a 4th cell type has been identified; these are round cells within the basal compartment of taste buds (Murray, 1973; Royer and Kinnamon, 1991; Taniguchi et al., 2005), and most if not all type IV cells are believed to express *Shh* (Miura et al., 2001; Miura et al., 2003; Miura et al., 2004; Miura

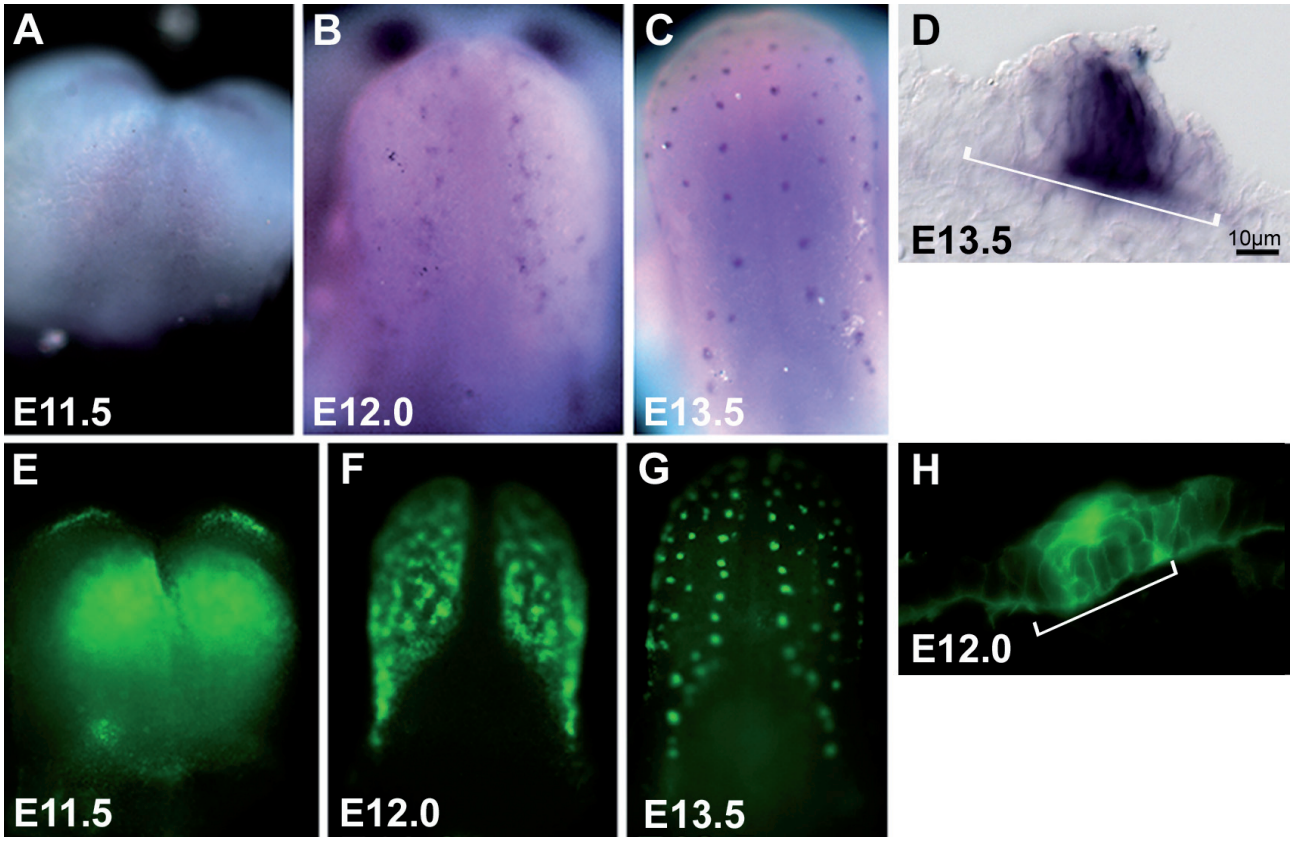

Fig. 2. - Shh expression in developing tongues. In situ hybridization (A-D) and protein expression (E-H) reveal Shh throughout the lingual epithelium at E11.5 (A, E). Shh resolves at E12.0 (B, F, H), and is restricted to the taste placodes by E13.0 (C, D, G). A-C. *Shh* mRNA (purple) in whole tongues at progressive developmental stages. D. An E13.5 tongue cryosection reveals *Shh* in a subset of epithelial cells within a developing taste papilla (white bracket). E-G. Whole mount tongues immunofluorescently stained for Shh protein (green) exhibit the same expression pattern as *Shh* mRNA. H. An immunostained tongue cryosection at E12.0 reveals Shh expression is coincident with the morphological extent of the placode (white bracket). Anterior is up A-C, E-G. Scale: D and H = 10 μm. Images courtesy of Dr. Shoba Thirumangalathu.

et al., 2005b). These cells are hypothesized to be a transient precursor cell population of taste buds that first occur in the embryonic Shh-expressing taste placodes (Nakayama et al., 2008). Shh-expressing type IV cells are not taste buds stem cells, as they are, like fusiform taste cells, postmitotic (Miura et al., 2004). Shh-expressing basal cells may represent an early differentiated phase of immature taste cells, given that BrdU pulse labeled *Shh*-expressing intragemmal basal cells peak in number roughly 24 hrs after their last perigemmal division (Miura et al., 2004). While the identity of taste cells descendent from Shh-expressing type IV cells has not been determined with complete certainty, our preliminary data suggest that at least type II cells are produced by this lineage (H. Miura, J. Liang and L.A. Barlow, unpublished results).

In addition to its expression at a discrete stage in taste cell differentiation, Shh may function within taste buds as a regulator of cell renewal. For example, Shh regulates hair growth and feather formation, as well as skin homeostasis (Sato et al., 1999; Chuong et al., 2000; Stenn and Paus, 2001; McKinnell et al., 2004; Athar et al., 2006). In these tissues, Shh functions as a positive regulator of cell proliferation, and could serve a similar role in taste epithelium, particularly since Ptch1-expressing Shh responsive cells are located in the perigemmal proliferative zone surrounding each bud (Miura et al., 2001).

The basal cells of taste buds seem to share some molecular and cellular properties with taste placode cells: Both express not only Shh but also Prox1 (Nakayama et al., 2008); likely are intermediate progenitor cells of taste buds; and are mitotically

silent (Mbiene and Roberts, 2003). However, it is also noteworthy to clarify differences between them: 1) The expression of Shh in the basal cells is strongly dependent on taste nerves in adults, while Shh-expressing taste placodes occur before innervation; 2) Cytokeratin 8(CK8)-like immunoreactivity is present in fusiform but not the basal cells in taste buds (Knapp et al., 1995), while taste placodes are CK8 positive (Mbiene and Roberts, 2003); and 3) The time window of Shh expression in taste placodes seems to be much longer than that in the basal cells in taste buds. It is unclear when and how theses differences manifest in Shh-expressing progenitor cells of taste buds during development. Some clues, however, may come from a sensitive period for the neural dependence of taste buds (Hosley et al., 1987). The number of taste buds developing in rat circumvallate papillae was reported to be largely dependent on innervation within 10 days after birth, suggesting that taste nerves may be involved in the conversion of the Shh-expressing cells from an embryonic to an adult state.

A number of other signaling factors and regulatory genes are expressed in adult taste buds, but their function, to date, has not been determined. However, conjecture is rampant as to what these gene products may be doing, based on their function(s) in other epithelial and neural systems. In addition to Shh, the Notch (N) pathway has been implicated in taste cell renewal, based on expression patterns of N receptors 1, 2, and 4, several transmembrane N ligands including Delta-like 1 (Dll-1) and Jagged 1 and 2, and known transcription factors of this signaling system, i.e., Mash1, Hes6 and Hes1 (Seta et al., 2003; Miura et al., 2005a; Seta et al., 2006a; Seta et al., 2006b; Ota et al., 2009). Mash1 expression is clearly associated with type III cells (Seta et al., 2006b), and may also be expressed by a subset of cells which eventually differentiate into type II taste cells (Miura et al., 2005a). Thus, the Notch pathway may regulate cell fate decisions during taste cell renewal.

Sox2 is a transcription factor essential for embryonic development and may function as a "master regulator" of stem cell multipotency in a number of tissues (Rizzino, 2009). In the taste system, Sox2 is required for embryonic taste bud development (Okubo et al., 2006), and is expressed in adult taste buds, in both immature taste cells and differentiated type I cells (Suzuki, 2008). Sox2 is also expressed in neural progenitors in the developing and adult nervous system (Ellis et al., 2004), where it functions to maintain neural progenitor state and regulate neural cell fate (Bylund et al., 2003; Graham et al., 2003; Episkopou, 2005). Given Sox2 is expressed both intragemmally and perigemmally in adult taste organs (Okubo et al., 2006; Suzuki, 2008; Okubo et al., 2009), this transcription factor may have a number of functions in taste cell renewal.

Taste bud homeostasis and the response(s) to injury

Under normal conditions, taste cell regeneration likely occurs at a consistent pace. However, these sensory cells are sensitive to insult, and taste buds themselves are impacted in a number of scenarios, which are relevant to human health.

Perhaps the most thoroughly investigated paradigm for studies of taste bud morphology is the denervation model. As early as the late 19th century, researchers have shown that differentiated taste buds are dependent upon an intact innervation (Vintschgau and Honigschmied, 1876; Torrey, 1934; Guth, 1958; Sollars et al., 2002; Oakley and Witt, 2004); when either the chorda tympani branch of the VIIth nerve, or the glossopharyngeal nerve (of cranial ganglion IX) is transected, fungiform taste buds of the anterior tongue, or circumvallate papilla taste buds, respectively, are reduced. The impact of denervation on fungiform taste buds appears to be less severe than on circumvallate; while the former are reduced in number, many albeit smaller taste buds remain (Whitehead et al., 1987; Oliver and Whitehead, 1992; Oakley et al., 1993; Sollars et al., 2002; Oakley and Witt, 2004; Guagliardo and Hill, 2007). By contrast, circumvallate taste buds disappear in the first few weeks following denervation (Wong et al., 1994; Seta et al., 1999; Miura et al., 2004), but will regenerate following nerve regrowth if the nerve sheath retains continuity (Guth, 1958; Uchida et al., 2003; Miura et al., 2004; Yee et al., 2005). While differentiated taste buds disappear or are reduced in denervated epithelium, the presumption is that the progenitor cells also require neural signals of some sort, in order to continue to provide immature cells to the taste buds. Thus, one hypothesis is that proliferation of the basal keratinocytes

surrounding taste buds should be reduced or stop altogether. However, to date, only a single study has tested this idea in denervated fungiform taste buds, and the data were inconclusive. Only a small reduction in the rate of cell renewal was detected in denervated taste buds (Oliver and Whitehead, 1992). However, a comparable analysis of proliferation in the more strongly affected circumvallate papilla might reveal how and when denervation impacts taste cell progenitors. As for human health relevance, both the glossopharyngeal and chorda tympani nerves can be damaged inadvertently during oral surgery (Gent et al., 2003; Klasser et al., 2008), and chronic otitis media (ear infection) can also result in chorda tympani damage and concomitant taste sensitivity problems (Bartoshuk et al., 1996; Gent et al., 2003; Sano et al., 2007; Felix et al., 2009). In each case, taste bud regeneration from the proliferative pool likely is reduced.

Head and neck cancer patients provide another clue as to the nature of taste bud regeneration. These patients receive a course of daily radiotherapy over the span of 6-7 weeks, designed to target the rapidly proliferating population of tumor cells. However, this paradigm also consistently causes a reduction in taste sensitivity in patients, resulting in reduced food intake and weight loss, and therefore an overall reduced quality of life (Nelson, 1998; Ruo Redda and Allis, 2006; Sandow et al., 2006; Yamashita et al., 2006). Using rodent models, radiation has been shown to cause a loss of taste buds and to some degree, taste sensitivity, in the weeks following dosing (Conger and Wells, 1969; Mossman et al., 1979; Nelson, 1998; Yamazaki et al., 2009), but the precise cell biological link between taste function and taste bud/taste nerve morphology has not been defined. While a number of potential mechanisms have been proposed, the most parsimonious of these is that reiterative (fractionated) radiotherapy results in the cumulative depletion of taste bud progenitors as opposed to direct injury of differentiated taste cells or the afferent nerve fibers, which innervate them. This model for taste bud regeneration is consistent with that for irradiated surface epithelium. In irradiated skin, proliferating cells are more vulnerable to radiation-induced DNA damage than are postmitotic cells, and thus the TA (transit amplifying) pool is initially most affected, while a smaller complement of slowly dividing progenitors are also impacted. Thus, immediately following a radiation dose, cell proliferation is quenched, as TA and progenitor cells either attempt to repair damaged DNA, or, if unsuccessful, undergo programmed cell death. With repeated radiation, an increasing percentage of both TA and progenitor cells is gradually lost, as are their progeny (Dorr et al., 2000; Potten et al., 2002). Whether a comparable scenario applies to taste buds remains to be tested.

Chemotherapy has also been reported to cause taste dysfunction in human patients who receive treatment for non-head and neck cancers (Ovesen et al., 1991; Minakata et al., 2002; Berteretche et al., 2004; Kiewe et al., 2004; Cheng, 2007; Wismer, 2008). Again, as rapidly dividing cells are targeted by these drugs, the presumption is that taste bud progenitor and TA cells are inadvertently affected, resulting in cell-depleted taste buds.

Finally, taste sensation is influenced by viral and bacterial infection (Heald et al., 1998; Bromley, 2000; Pribitkin et al., 2003), likely due to inflammation that is triggered by these pathogens (Wang et al., 2007; Wang et al., 2009; Welge-Luessen, 2009). In fact, Wang and colleagues (Wang et al., 2007; Wang et al., 2009) have recently shown that experimental bacterial or viral infection of mice causes a specific interferon response in taste buds, and ultimately results in increased taste cell apoptosis. This result hints at an additional level of regulation of taste bud regeneration, where differentiated taste cells are the target population.

Acknowledgements

The authors wish to thank the Rocky Mountain Taste and Smell Center funded by a P30 grant DC004657 from NIDCD/NIH to Dr. Diego Restrepo. LAB is funded by DC003947 and DC008373 from NIDCD/NIH. We gratefully acknowledge our lab and Center colleagues for their intellectual input and valuable critique of our work.

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