Feedback control of size, cellular composition, and regeneration speed in neural epithelia: experimental and computational analysis

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In many tissues, cell proliferation and differentiation are dynamically regulated to achieve goals such as robust size control, short generation time, rapid regeneration, appropriate ratios of cell types, and minimal numbers of "resting" progenitor cells. The molecular mechanisms underlying such performance are slowly emerging: In mammalian liver and muscle, evidence points to negative feedback loops, by which molecules made by "terminally" differentiated cells inhibit progenitor cell proliferation. In other tissues, cell communication pathways such as *Notch* signaling are involved in both diversifying the types of cells produced and regulating proliferation. Are such mechanisms sufficient to produce the sophisticated proliferative control observed in epithelial tissues? If so, what are the necessary preconditions, and how is control achieved?

To investigate these questions, we focus on the Olfactory Epithelium (OE) of the mouse. The primary cells of the OE are neurons that relay olfactory information from the nose to the brain. The OE is formed rapidly during embryonic development, and produces neurons throughout life at a rate that balances cell death. In response to manipulations that kill neurons, progenitor cell populations quickly become more proliferative and increase in size, leading to rapid restoration of neuron number.

OE progenitor cells are classified according to their expression of genes that encode lineage stage-specific transcription factors: Neurons derive from a cell ("the immediate neuronal progenitor", or INP) that expresses *Ngn1*; this in turn derives from a cell that expresses *Mash1,* which itself derives from a stem cell that expresses *Sox2*. INPs and *Mash1*$^+$ cells are "transit amplifying cells", i.e. their divisions result either in replication (production of more of the same cell type) or differentiation (production of cells of the next lineage stage). Analysis of OE under experimental conditions—in tissue culture, during development, in mutant backgrounds, during regeneration—has revealed much about the molecules that regulate its growth. At least two molecules released by OE cells feed back to inhibit progression of progenitor cells through the neuronal lineage: GDF11, which is produced by INPs and immature neurons, acts solely on INPs; activin B, which is produced throughout the OE, acts on stem and *Mash1*$^+$ cells.

We have asked whether quantitative models that incorporate GDF11- and activin-dependent feedback can both fit experimental data and shed light on control strategies. For example,

analysis of simple ODE models reveals that the molecular mechanism initially proposed for GDF11—decreasing or halting cell cycle progression—neither fits the phenotype of *Gdf11*$^{-/-}$ mice, nor contributes usefully to size regulation and rapid regeneration. In contrast, models in which GDF11 lowers the replication probability of INPs achieve both goals. Using this information, we performed tissue culture experiments demonstrating that GDF11 indeed exploits the second mechanism. The utility of combining activin- and GDF11-dependent feedback in the same tissue has also been explored computationally, and will be discussed. Because the molecules and mechanisms that regulate proliferation and size in the OE are also utilized in other tissues, the results of this work are likely to apply to many epithelial and neural systems.