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Equal opportunities in stemness

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Abstract

Tissue renewal requires proliferative progenitors with long-lasting potential. Designated stem cells within specialized niches are considered to be the primary mechanism for this requirement. Recent studies show that dispersed equipotent progenitors are sufficient to account for fast-paced cellular dynamics in skin oil glands and fetal gut epithelium.

To maintain a stable steady state, tissues with a high rate of cellular wear-and-tear require fast mitotic activity from their progenitors. Thus, robust mechanisms for long-term preservation of the progenitor state are required to avoid progenitor exhaustion and tissue collapse. One such strategy is to designate groups of specialized stem cells into anatomic niches whose signalling environment supports stemness (Figure 1). Commonly, such designated stem cells divide infrequently to produce short-lived, transit amplifying progeny that, in turn, divide rapidly to generate new differentiated cells for the tissue[1]. Transit amplifying cells often relocate into their own distinct signalling microenvironment, which supports fast division and differentiation, but not stemness. This tissue organization strategy is fairly prevalent, and examples include hair follicles, where stem cells reside in the bulge[2], and the small intestine, where stem cells are located at the crypt base[3].

An alternative strategy, however, exists in some other fast-renewing tissues. For example, in skin epidermis, a clear distinction between long-lasting cells and rapidly-dividing cells is lacking, in terms of their anatomic distribution, cell cycle properties, and marker genes (Figure 1). Indeed, skin epidermis is maintained by so-called equipotent progenitors[4], that

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Competing interests

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both proliferate at a high rate, but also produce long-lasting clones – a key property of stem cells. At the population level, equipotency allows for a tissue to remain in a steady-state, even though at the individual level some cellular clones expand, whereas others shrink and even disappear, a phenomenon known as neutral drift[1]. When such clonal competition occurs in small, isolated tissue compartments, one clone eventually outcompetes the others, a phenomenon known as monoclonal conversion[1].

In a study in this issue of *Nature Cell Biology*, Andersen, Hannezo, Ulyanchenko *et al.*[5] examined whether skin oil glands, also called sebaceous glands, are maintained by designated stem cells or equipotent progenitors. These glands are functionally distinct units of the skin, tasked with producing a lipid-rich secretion, which waterproofs and protects skin from the outside. Lobe-like in shape, sebaceous glands are intimately connected to hair follicles via ducts. Yet, unlike hair follicles, they do not undergo obvious growth cycles and constantly output their secretion instead[6]. Previous lineage studies provided evidence both for equipotent progenitors residing within the gland[7], as well as for designated stem cells near[8, 9] and outside the duct[10], which send short-lived progeny into the gland. By quantifying fate mapping outcomes *in vivo* and correlating them with mathematical model predictions on clone size dynamics, the authors concluded that the steady-state renewal of sebaceous glands in adult mice occurs via equipotent basal progenitors, and independently of neighboring stem cell populations. Single-cell fate mapping assays, in which one progenitor per gland was marked at the beginning of an experiment, supported this conclusion and showed progressive monoclonal conversion of glands. In these assays, labeled cell clones lacked clear directional bias, suggesting that clonogenic gland progenitors are equally distributed. Experimentally measured clonal data was most consistent with simulations of a mathematical model that assumes an equipotent population of dividing progenitors stochastically choosing between alternative fates – to either differentiate or divide into two new progenitors.

Another recent study in *Nature* shows that intestinal epithelial progenitors remain equipotent during the phase of fetal gut morphogenesis, and prior to the establishment of adult villus-crypt anatomy[11]. The fetal intestinal epithelium in mice first becomes patterned into primordial villi, which then rapidly increase in number via the process of villification during late embryonic and early postnatal periods, reaching adult villi density by approximately day five after birth[11]. Rather than exclusively forming in the intervillus space, many new villi develop via fission of earlier-born villi coupled with lateral cell rearrangements across neighboring villi and intervillus regions. Under such mechanism, all fetal intestinal progenitors, irrespective of their initial anatomic position, have equal opportunity to become adult intestinal stem cells of the crypt, and their final fate is determined by the ultimate anatomic position that cells assume at the end of villification. Thus, it seems that maintaining equipotency or, at least, making early fate choices more easily reversible is crucial for normal gut morphogenesis.

Considering that both strategies have been observed during formation and maintenance of different tissues, which benefits does each strategy offer? So far, equipotency has been the primary mechanism observed in expanding tissues with highly-curved spatial structures, such as in the developing gut[11]. Only an equipotency model faithfully recapitulates the

progressive morphogenesis of new villi across the entire fetal gut, including the tips of preexisting villi. A similar strategy likely operates during hair morphogenesis in fetal skin: new hair primordia form from embryonic epidermal progenitors via self-organized patterning with no apparent restrictions on the spatial placement of primordia[12]. Similar to morphogenesis, regeneration might also benefit from progenitor equipotency to enhance robustness. By reactivating an embryonic-like program, the epidermis in large skin wounds can regenerate new hair follicles without fully relying on lineage contribution from preexisting hair-follicle-fated stem cells[13]. With equipotency, the basal epidermal progenitors in skin wounds are likely competent of making new hair follicles, irrespective of their prior lineage identity in unwounded skin. Beyond morphogenesis and wound repair, equipotency can be a preferred mode of organization for relatively simple lineages, such as epidermal or sebaceous gland lineages, in which the number of cell types is small and their relationship is linear.

Conversely, the existence of designated and spatially segregated stem cells can be beneficial for complex lineages, consisting of many branching points and multiple terminally-differentiated cell types, as found in the hair follicle and adult intestine. Spatial segregation of stem cells away from their progeny can localize differentiation-promoting signalling without interfering with the stem cell niche signalling. Notably, major differentiation events in the hair follicle lineage occur at its base, in the so-called hair matrix, and at a distance from the *bona fide* stem cell niche. Another benefit that designated stem cells in specialized niches may offer is to gain stronger, on-demand temporal control over lineage production. For example, placing hair follicle stem cells into a spatially defined and quiescent-signal-enriched niche allows for extended, often months-long resting phases between active hair growth cycles[14]. This adaptation potentially provides animals with an energy conservation advantage. Functional fur can consist entirely of old hairs without requiring a constant resupply of newly growing hairs. Such extended quiescence might be more difficult to enforce on many equipotent progenitors interspersed in space. Although both strategies may provide different benefits for different purposes, there is a possibility they may coexist. In support of this theory would be a recent study by Feldman *et al.*[9] that argued for the existence of previously debated BLIMP1$^+$ sebaceous gland stem cells[7, 8, 10] by showing that *in vitro* differentiated sebaceous gland organoids form with high efficiency from single BLIMP1$^+$ cells, which also maintain long-term passaging potential.

What drives cellular decision to differentiate or to renew? The study by Andersen, Hannezo, Ulyanchenko *et al.*[5] also sheds light on the potential mechanism that drives decision making in an equipotent progenitor population. Mathematical modeling convincingly argues that stochastic cell fate decisions can be predicted using parameters such as division rate and fate probability, which are sufficient to faithfully account for the observed steady-state renewal of sebaceous glands by equipotent progenitors. During tissue morphogenesis or regeneration, such parameters must dynamically adjust their values as required to regulate differentiation *vs.* self-renewal. Feedback regulation imposed on progenitor cells by their environment may potentially robustly control these parameters[15].

Intriguingly, the authors also performed experiments with oncogene-overexpressing mice, in which sebaceous glands substantially enlarged, driven by gland progenitors biasing toward

self-renewal[5]. Concurrent with gland enlargement, stiffness and molecular composition of the surrounding extracellular matrix changed prominently. An open question is whether the underlying extracellular matrix provides biophysical and signalling inputs to progenitors to guide their decisions. Interestingly, a recent study by Liu *et al.*[16] showed that levels of collagen XVII in the basement membrane of skin epidermis naturally fluctuate, in part as a result of proteolysis, and epidermal progenitors exposed to high collagen XVII levels commonly self-renew by dividing parallel to skin plane. Conversely, those subjected to decreased collagen XVII preferentially divide perpendicularly and their clones are reduced and outcompeted over time.

Overall, these observations suggest that a stochastic-like fate selection by individual equipotent progenitors may be underpinned by complex inputs to cells from their "information space", which may include extracellular matrix, cell-cell contact cues and soluble growth factor signals from neighboring cells, including other progenitors and immune cells (Figure 1). Highly curved spatial structures, such as the gut, are particularly suitable to provide strong physical and mechanical cues to the progenitors. Future studies that simultaneously measure cellular dynamics with one or several information inputs, preferably at single-cell resolution, will advance our understanding on cell fate control in equipotency. In addition, skin with its many layers and patterned structures, offers a particularly fertile system for conducting multiscale mathematical modeling to dissect cell fate control[17]. The study by Andersen, Hannezo, Ulyanchenko *et al.*[5] provides a prime successful example on how the synergy between modeling and experimentations leads to new discoveries in stem cell biology.

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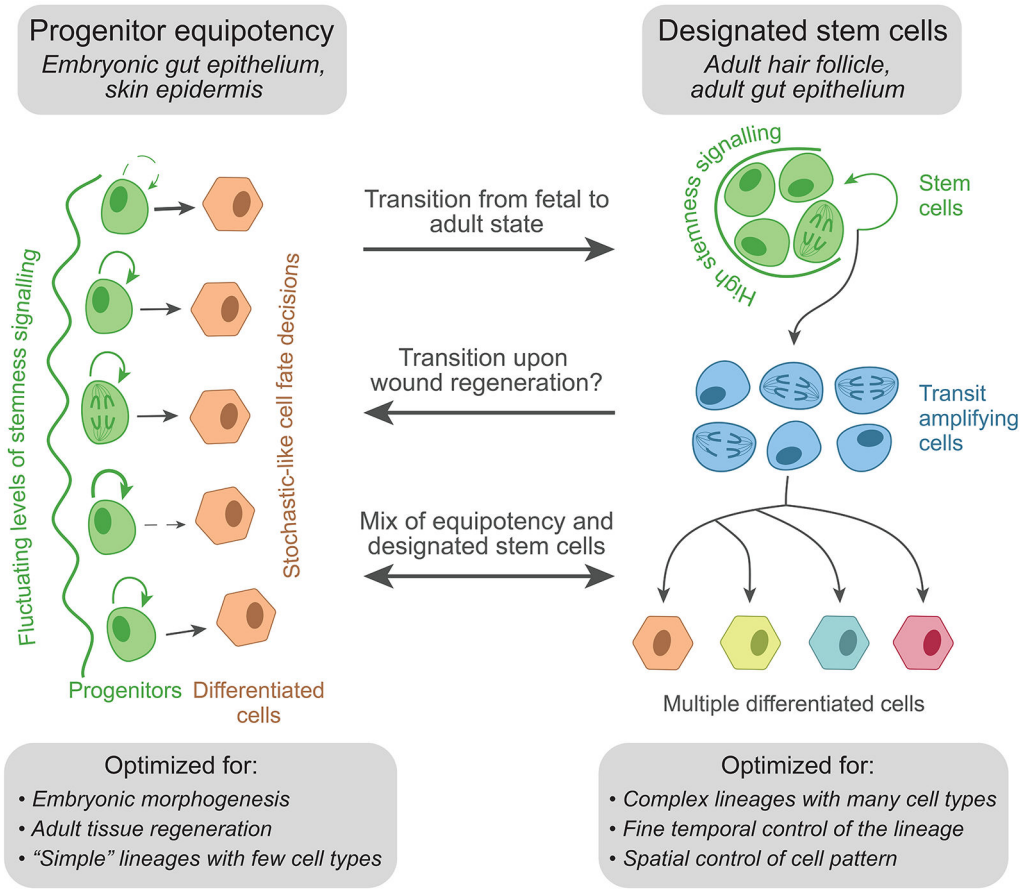

Figure 1: Equipotency and designated stem cells as complementary strategies for lineage maintenance.

Long-term tissue maintenance can be accomplished either with many dispersed equipotent progenitors (left) or with rare designated stem cells residing in specialized niches (right). Evolved to divide infrequently and persist long-term, designated stem cells give rise to transit amplifying progeny (blue on the right) that move out of the niche, where they rapidly proliferate and differentiate, often into multiple cell types. With equipotency, tissue is maintained by many actively dividing and, simultaneously, long-lasting progenitors. While in their niches, stem cells self-renew efficiently as a result of specialized signalling. Self-renewal of equipotent progenitors is stochastic-like – a phenomenon caused by fluctuating soluble, extracellular matrix and cell-cell contact cues in the extracellular "information space" (zig-zag green line on the left). Both lineage maintenance strategies have their distinct advantages (text boxes at the bottom). Further, strategies can switch during tissue development and regeneration and also, likely, complement each other.