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Plasticity of epithelial stem cells in tissue regeneration

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Abstract

Tissues rely upon stem cells for homeostasis and repair. Recent studies show that the fate and multilineage potential of epithelial stem cells can change depending on whether a stem cell exists within its resident niche and responds to normal tissue homeostasis, whether it is mobilized to repair a wound, or whether it is taken from its niche and challenged to de novo tissue morphogenesis after transplantation. In this Review, we discuss how different populations of naturally lineage-restricted stem cells and committed progenitors can display remarkable plasticity and reversibility and reacquire long-term self-renewing capacities and multilineage differentiation potential during physiological and regenerative conditions. We also discuss the implications of cellular plasticity for regenerative medicine and for cancer.

Epithelia are cellular sheets often residing at the interface between the external environment and body organs, including skin, gut, airway tracts, kidney, liver, mammary glands, and prostate. They perform a diverse array of physiological functions, including the ability to retain body fluids, absorb nutrients, filter and eliminate toxic by-products of metabolism, and regulate body temperature. Each epithelium is morphologically and molecularly suited to its particular task, a feature that necessitates specialized cell lineages.

Most epithelia replenish themselves through a process called tissue homeostasis, in which the number of cell divisions within a tissue compensates for the number of cells lost (1). Tissue homeostasis is ensured by the existence of stem cells (SCs) located within specialized microenvironments, referred to as niches. Each niche is tailored to accommodate the regeneration needs of the tissue (2).

The skin epidermis and its appendages (hair follicles, sebaceous glands, and sweat glands) harbor spatially distinct SC niches. The innermost (basal) layer of interfollicular epidermis (IFE) harbors proliferative progenitors, which generate the stratified layers of the skin barrier. Every few weeks, the IFE renews itself almost entirely, placing a constant demand on its SCs. Sebaceous glands (SGs) also turnover continuously during adult homeostasis. By contrast, hair follicles (HFs) cycle through bouts of hair growth and degeneration,

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necessitating only periodic use of SCs, whereas sweat gland (SwG) cells are mostly quiescent (Fig. 1A).

Other epithelia also have distinct requirements for tissue homeostasis, which must be met by their resident SCs. In the small intestine, the epithelium is organized into a crypto-villus unit (Fig. 1B). The crypt is composed of columnar basal cells (CBCs) intermingled with Paneth cells at the crypt base; an overlying compartment of transit-amplifying (TA) cells divides several times and then terminally differentiates to generate the absorptive and secretory cells of the villus. Villus cells are subsequently shed into the lumen (3), which results in continual turnover of the entire crypt every 3 to 5 days. CBCs, now known to be SCs, fuel the process.

Functionally validating stemness of epithelial cells in vitro

Different methods have been elaborated throughout the years to study the fate, renewal, and differentiation potential of epithelial SCs. The first functional demonstration of an epithelial SC was made when methods were identified to culture human epidermal keratinocytes under conditions where they could be maintained and propagated for hundreds of generations without losing stemness (4). When grown from an unaffected region of a burn patient, expanded epidermal cultures could be stably engrafted onto the damaged skin (5). Engrafted epidermis did not develop cancer or other abnormalities, which indicated that, under the right conditions—in this case, coculture with irradiated dermal fibroblasts—in vitro SC expansion and differentiation can be achieved without deleterious consequence.

The requirement of dermal neighbors for successful culturing of epidermal SCs highlights the reliance of SCs on cross-talk with their niche microenvironment. Indeed, by elucidating key heterologous niche components and/or the cross-talk involved, SCs from many different epithelia have since been successfully cultured. For intestinal stem cells (ISCs), it took BMP and Notch inhibition together with Wnt activation to recapitulate in vitro the long-term proliferative capacity and multipotency normally conferred to ISCs by their niche (6). These studies underscore the complexities of signaling circuitry governing SC behavior and the need to understand this to maintain SCs in the absence of other heterologous cell types in vitro.

Identifying epithelial SCs in vivo and probing their roles in tissue homeostasis

HF homeostasis

Lineage tracing entails the genetic marking of one or a group of cells in their normal physiological context in a way that their subsequent progeny retain marker expression. This method is powerful in evaluating the contribution of SCs to tissue homeostasis (1). The fluctuations of HFs through synchronized bouts of hair growth and inactivity present an interesting variation on this theme (Fig. 2A). Before modern-day genetics, cells with proliferative potential that spent extended periods in quiescence were marked and monitored by nucleotide analog pulse-chase experiments. Such label-retaining cells (LRCs) reside at the base of the resting HF, a region now referred to as the bulge and its associated hair germ (HG) (7). LRCs are SCs, as demonstrated by using a regulatable fluorescent histone to label

LRCs and monitor their cell divisions, as well as lineage tracing to follow their fate (8–12) (Fig. 2B).

Both bulge and HG share many molecular features of stemness, including expression of *Lgr5* and *Sox9* (12, 13). However, HG cells are always the first to be activated at the start of each new hair cycle, and they undergo more divisions than bulge cells (13). Their close proximity to the underlying mesenchymal signaling center, the dermal papillae (DP), functions in dictating this early response.

Activated HG cells do not maintain stemness in vitro (13), and in vivo, they generate the TA cells that produce the hair and its channel (14, 15). By contrast, once the new hair cycle initiates, some bulge cells leave their niche and form an inverse proliferative gradient along the emerging outer root sheath (ORS). Early in the hair-growth phase, TA cells stimulate remaining bulge cells to proliferate and replenish the niche (15). ORS cells closest to the bulge return to quiescence soon thereafter and form a new bulge and HG for the next cycle (12, 16). The ability of bulge and HG SCs to generate the seven different HF lineages underscores their multilineage potency. Additionally, even though bulge normally gives rise to HG, HG can replenish an empty bulge niche, as shown by laser ablation and live imaging (16), which underscores their close relation and capacity to inter-convert when necessary (see below).

Although the above studies disclose insights into the behavior and maintenance of cycling HFs, lineage tracings reveal the existence of at least two additional SC populations—SG and infundibulum—within the noncycling HF segment. SGs are maintained by unipotent *Lgr6*$^+$*Lrig1*$^+$ SCs that arise from *Blimp1*-expressing progenitors (17). In adults, Lgr6-expressing cells mark and sustain SGs (18, 19), whereas Lrig1 expression extends to SCs fueling infundibulum homeostasis (19) (Fig. 2A). One other SC population in the upper bulge region has been suggested on the basis of its encasement by sensory nerve sheaths (20). Whether these cells represent an independent pool of functional SCs remains unresolved.

A sharp boundary exists between infundibulum-derived *Lrig1*$^+$ cells and IFE (19), and little if any contribution to the IFE has been observed by the various adult SCs thus far identified in the HF (9, 10, 19, 21–23) (Fig. 2A). This argues against the prior view that a single “master” SC population presides over all skin lineages, as initially postulated based upon embryonic *Lgr6*-Cre lineage tracing (18). Indeed, the paradigm for segmental-tissue governance by SC units has ancient origins, as, like the HF, *Drosophila* intestinal epithelium is also compartmentalized into discrete units maintained by separate SC populations (24).

IFE homeostasis

The IFE is maintained by juxtaposition of small units of proliferation containing stem and/or progenitor cells (1). During embryogenesis, the single layer of K14$^+$ epidermal basal progenitors undergoes a spindle orientation shift from >90% symmetric to ~70% asymmetric cell divisions, which leaves one daughter in the basal layer and one suprabasal differentiating daughter cell (25). Postnatally, SCs and transient progenitors coexist within the IFE basal layer, and both express K14 but can be distinguished by their survival rate,

mode of division, gene expression, and ability to respond to tissue damage (26) (Fig. 2A). Basal progenitors targeted by *Ah*-Cre^{ER} (27, 28), *Inv*-Cre^{ER} (26), and possibly *Axin2*-Cre^{ER} (29), divide mostly asymmetrically, whereas K14^{+} basal SCs are integrin-rich and divide mostly symmetrically to generate two long-lived daughters (26, 30). Although the exact nature of the imbalance between SC and progenitor division is not yet clear, each SC-progenitor division must also be accompanied by some differentiation, driven in part by Notch signaling (31–34).

Crypt homeostasis: A one-cell–winner competition

Ultrastructural analyses and proliferative capacity of the intestinal crypt led to the initial hypothesis that CBCs are ISCs (35) (Fig. 1B). Subsequent assignment of stemness favored cells at the +4 position, given their mode of chromosome segregation (36) and higher resistance to DNA damage–induced cell death (37). Lineage tracings of +4 CBCs with *Bmi1*, *mTER*, and *Hopx*-Cre^{ER} and 0→+3 CBCs with *Lgr5*-Cre^{ER} revealed that all crypt CBCs behave as interconvertible multipotent ISCs (38–42) (Fig. 3, A to C). This is further exemplified by diphtheria toxin (DT)–targeted ablation of *Lgr5*-expressing cells, which does not impair intestinal homeostasis (43) (Fig. 3D). Thus, despite their markedly different regenerative demands, both HF and intestine have spatially discrete interconvertible SCs existing in quiescent and primed and/or activated states (bulge and HG versus +4 and 0→+3 crypt cells).

Although it was initially proposed that all *Lgr5*$^{+}$ ISCs cycle rapidly (38), a recent study using yellow fluorescent protein and histone H2B label–retention assays reveals that ~20% of *Lgr5*-expressing cells cycle less frequently, exhibit a mixed ISC–Paneth cell transcriptional profile, and differentiate into Paneth and neuro-endocrine cells (44). Although these slow-cycling cells do not contribute to crypt homeostasis during physiological conditions, they can form organoids in vitro with comparable efficiencies as rapidly cycling *Lgr5*$^{+}$ ISCs and can mediate crypt regeneration after injuries (44).

Despite these behavioral distinctions among ISCs, their cellular dynamics within the crypt systematically drift toward monoclonality (45–49). Thus, over time, each crypt-villus unit derives from a single ISC (Fig. 3E). The mechanism leading to crypt monoclonality is thought to derive from neutral competition between an equipotent pool of ISCs that includes both *Lgr5* and *Bmi1-Hopx* ISCs (49). In contrast to epidermis (in which progenitors divide mostly asymmetrically), ISCs are thought to divide symmetrically and compete for niche space (48, 49). Based initially on *Lgr5* expression and mathematical modeling (48, 49) and subsequently on a novel method of continuous labeling (50), it is estimated that between 5 and 16 *Lgr5*$^{+}$ ISCs compete with each other for niche space in a neutral drift manner.

Live imaging of *Lgr5*-Cre^{ER} lineage tracing has recently enabled the visualization of these displacements during ISC divisions. Ironically, with each division, ISCs reorganize their position within the crypt, which underscores their interconvertibility (42) (Fig. 3, B and C). In the end, one ISC outcompetes the others. It will be interesting to see in the future whether such competition happens in other SC niches and how the competition unfolds at a molecular level.

Crypt monoclonality underscores the multi-lineage potential of ISCs. Increasing evidence suggests that their fate choices are rooted at the transcriptional level. Thus, equipotent progenitors undergoing Notch-mediated lateral inhibition quickly enable distinct—in this case, reversible—cell fates to establish progenitor cell lineages as either absorptive or secretory. Moreover, *Atoh1*, a secretory-specific transcription factor expressed by ISCs, controls lateral inhibition through *Dll* genes and also drives expression of secretory lineage genes, which suggests that intestinal crypt lineage plasticity involves a lineage-restricted transcription factor expressed by multipotent ISCs (51).

Switch from multipotency to unipotency in glandular epithelia

Mammary glands (MGs), SwGs, and prostate glands are composed of an inner luminal layer, surrounded by an outer layer of myoepithelial and/or basal cells. Their morphogenesis begins late in embryogenesis and is completed postnatally.

As judged by lineage tracing, both MGs and SwGs and their associated ducts originate from K14-expressing multipotent embryonic epidermal progenitors (52–54). Although it was recently suggested that some bipotent SCs persist within the myoepithelial layer (55), myoepithelial and luminal lineages of MGs, SwGs, and prostate are largely maintained postnatally by distinct pools of unipotent SCs (52–54, 56–60) (Fig. 4A).

In the adult, both myoepithelial and luminal epithelial SwG SCs display very little turnover during homeostasis (53). By contrast, MG's SCs exert tremendous tissue-generating potential during puberty and pregnancy, making them especially well suited for studying glandular SC biology (52, 54). Heterogeneity within luminal and alveolar compartments has been seen with *Notch2*-Cre^{ER} and *Notch3*-Cre^{ER} lineage tracing (59, 60). Whether these two luminal populations can interconvert remains unknown.

During prostate development, clonal analyses also suggest heterogeneity, this time in the basal compartment. Bipotent and unipotent basal progenitors have been identified, as well as basal cells already committed to the luminal lineage (61). Whether this apparent cellular heterogeneity reflects the existence of distinct progenitors or, alternatively, stochastic fate decisions of a single multipotent progenitor remains to be determined (61).

Altogether, lineage-tracing experiments performed in different glandular epithelia show that they initially develop from multipotent progenitors which are progressively replaced by unipotent SCs for adult tissue homeostasis and repair (52, 53, 56, 61). However, despite similar histologies and SC behaviors, their multipotency → unipotency switch occurs at different times during development (52, 53, 56–58, 61).

Transient plasticity of epithelial SC during tissue repair

Over evolution, homeostasis has been optimized for different SC compartments to replace local cells that die. However, if one SC compartment is damaged, other SCs must be recruited to repair the injury. A series of recent studies reveals that the fate and differentiation potential of epithelial cells can broaden during tissue regeneration after wounding. In some cases, unipotent progenitors acquire multipotency, whereas, in others,

normally committed cells revert back to a SC-like state to ensure tissue regeneration. The cellular plasticity and reversibility observed in adult epithelial tissues have not been associated with "transdifferentiation" into completely unrelated fates but rather with contribution to the repair of the tissue from which the cells originated. In this regard, the plasticity seems to arise through a process of dedifferentiation and/or redifferentiation.

How SCs respond to injuries and repair tissue wounds varies dramatically depending not only on the particular SC niche but also its proximity to the wound. In SwG cells, for example, where four different unipotent progenitors exist (53), luminal and myoepithelial progenitors are mobilized, but these SCs act unipotently in mediating tissue regeneration, at least under conditions where luminal or myoepithelial progenitors are selectively killed (53). Although these findings illustrate the ability of different SC compartments to mobilize in response to different types of injuries, each SC niche knows its own job and does not carry out the job of other resident niches.

By monitoring the fate of early IFE progeny during wound repair, signs of transient plasticity begin to surface. Thus, although long-lived IFE SCs are recruited to the wound region and stably contribute to reepithelialization, short-lived *involucrin*$^+$ IFE progenitors also migrate to wound sites. Within a month, most *involucrin*$^+$-derived progeny terminally differentiate (26), which suggests that lineage reversion is not sustained long-term (Fig. 5A). The apparent transient nature of lineage reversion observed in IFE contrasts with esophagus, where progenitors seem to change their mode of proliferation in repairing incisional wounds (62). Whether this difference is attributed to the type and/or severity of wound (incisional versus full thickness) or a fundamental difference in SC behaviors remains to be addressed.

Transient plasticity has also been reported for adult HF SCs in response to injury. In superficial skin wounds, bulge and infundibulum SCs migrate upward, proliferate, and participate in the epidermal repair process (8, 19, 21, 22, 63) (Fig. 5, B and C). Through mechanisms presently unknown, migrating HF SCs lose HF markers and adopt an IFE differentiation program. However, unlike neonatal skin, most of these cells do not seem to persist long-term within IFE (19, 63, 64). In this regard, they act more like a cellular bandage, which perhaps analogously to *involucrin*$^+$ IFE progenitors (26), are quick to respond but are eventually replaced by IFE SCs and their progeny.

Two relatively recent strategies to kill resident SCs—either laser-ablating them or ablating them through DT expression—have proven to be powerful methods to extricate SCs from their niches and examine the consequences. Initially shown for *Drosophila* germ SCs (65, 66), it is now well established that when mammalian epithelial SCs are ablated, the empty niches can recruit and induce normally committed cells to proliferate and revert back to a stemlike state.

A particularly elegant demonstration of this paradigm was made by coupling live imaging with laser-mediated cell lineage ablation of different HF populations (14, 16). The cellular plasticity within the bulge HF SC niche was documented by illustrating that bulge and HG cells can interconvert when one of these compartments is emptied (16, 67) (Fig. 5D). It is noteworthy that cells located in the upper bulge region, the so-called "junctional zone" SCs,

could also replenish the bulge niche after bulge SC ablation (16). Although future studies will be necessary to more closely examine the long-term capacity to interconvert into each other's fate and restore tissue function after injury, these findings capture the plasticity displayed by distinct skin epithelial SC compartments after injuries.

The microenvironment controls the fate of epithelial SCs

It has long been observed that when SCs are taken out of context and transplanted, either directly or after cell culture, they exhibit greater multipotency in their new microenvironment. Thus, upon engraftment to immunocompromised mice, freshly isolated bulge cells (9, 68) or clonal progeny of single bulge cells (69, 70) each generate not only HFs, but also IFE and SGs long-term (Fig. 2B). This is also true for isthmus and SG SCs (71, 72). Analogously, when normally unipotent SwG, MG, or prostate basal or myoepithelial SCs are purified and engrafted de novo, they generate entire functional glands (52, 53, 73–76).

When unipotent MG myoepithelial cells are transplanted into mammary mesenchyme of pregnant mice, they can reform a functional MG (52) (Fig. 4B), which demonstrates the plasticity of unipotent myoepithelial cells during regenerative conditions. Note that MG myoepithelial cells can also generate MGs when engrafted to shoulder pads, whereas SwG myoepithelial cells generate SwGs in virgin mammary fat pads (53). These findings suggest that for some adult progenitors, once identity is established, they take longer to respond to environmental and systemic programming factors. By contrast, when progenitors form tissue de novo during embryonic development, they have yet to receive the epigenetic marks that restrict their fates.

Similarly, after culture in vitro, marked thymic epithelial cells can be mixed with embryonic thymus and transplanted underneath the kidney capsule, where they integrate into the thymic network and differentiate into functional thymic epithelial cells (77). However, when the same cultured thymic epithelial cells are transplanted together with skin mesenchyme onto back skin, they differentiate into all epidermal lineages including HF and IFE (77). This plasticity in SC behavior appears to become more permanent with subsequent transplantations, illustrating how the microenvironment can instruct these cells to adopt very different fates.

A hint that adult epithelial cells may be able to undergo permanent fate conversions in vivo comes from monitoring IFE behavior after massive wounding. In this case, the IFE was reported to regenerate HFs, which is something it never does during homeostasis (78). It has long been known that transgenic β-catenin stabilization, the output of a Wnt signal, is sufficient to reprogram $K14^+$ IFE into HFs replete with their own DP (79). Overexpressing the hedgehog pathway also stimulates IFE to HF progenitor reprogramming, but in this case, differentiation becomes suppressed at the expense of hyperproliferation, which leads to basal cell carcinoma (80, 81).

Reversing fates: Converting committed progeny to SCs

Although the ability of adult epithelial SCs to acquire different lineage fates seems remarkable, several studies have recently suggested that committed epithelial lineage cells may have the capacity to acquire stemness. During normal homeostasis in the intestine, Delta-like 1 (*Dll1*)–expressing cells (82), or slow-cycling *Lgr5*$^{+}$ cells (44), are both short-lived Lgr5-derived progeny committed to the secretory lineage. However, after γ-irradiation–induced tissue damage, these normally committed Dll1^{+} progenitors appear to revert back to ISCs (82) and contribute to intestinal regeneration (Fig. 6, A and B). Similarly, when Dll1^{+} progenitors are purified and placed in Wnt3a-supplemented cultures, they form gut organoids containing *Lgr5*$^{+}$ SCs and all intestinal lineages (82), which supports the idea that they revert into a stemlike state. How Wnt signaling might influence the reversion process in vivo is a yet-unaddressed intriguing question. Whether these reserve cells are sufficient to be functionally relevant in the context of tissue repair is still unclear, as γ-irradiation–induced intestinal epithelial regeneration does not occur after *Lgr5* ablation (Fig. 6C) (83).

Another example of plasticity stems from recent lineage tracing of committed secretory cells in the lung (84), which can revert into stable and functional basal SCs in vivo if all airway SCs are ablated (85) (Fig. 7). In this case, it was shown that these dedifferentiated cells can respond to epithelial injury and repair injuries equivalently to their endogenous SC counterparts. By contrast, direct contact with a single basal SC was sufficient to prevent secretory cell dedifferentiation, suggestive of negative cross-talk between SCs and committed progeny. Overall, the propensity of committed cells to dedifferentiate is typically inversely correlated to their state of maturity.

The ability of a priori differentiated cells to be reprogrammed and interconvert into SCs has also been illustrated for stomach (86). The stomach epithelium is composed of an upper part of rapidly renewing cells, a middle zone, the isthmus that actively proliferates, and a bottom zone that contains two cell types (parietal and chief cells) with very low cellular turnover (87). Lineage tracing revealed that *Sox2*-expressing cells in the isthmus region are responsible for the homeostasis of the glandular stomach, giving rise to all stomach lineages (88). Through lineage tracing using *Troy*-Cre^{ER} to target differentiated parietal and chief cells (86), it was reported that progeny of some Troy cells slowly expand and reach the top of the gland after 6 months of chase, which shows that these cells play only a very minor role during homeostasis. However, the Troy cells can be cultured long-term as multipotent organoids in vitro and expand severalfold after tissue damage in vivo, suggestive of their ability to aid in repair of stomach injuries (86).

After acute injuries, liver and pancreatic beta-cell regeneration seems to involve self-duplication of differentiated cells (89, 90). In contrast, chronic and severe hepatic injuries stimulate mature hepatocytes and/or biliary cells to dedifferentiate into bipotent progenitor state–expressing SC markers, such as *Lgr5*, that mediate liver regeneration through their proliferation and redifferentiation (91).

Altogether, these remarkable studies point to the view that, under certain nonhomeostatic conditions, differentiated cells dedifferentiate, revert back to a SC-like fate, and participate in tissue repair. In particular, this seems to happen after severe injury, a situation where the tissue must respond quickly and creatively to ensure animal survival.

Reversibility of lineage differentiation and SC plasticity during tumorigenesis

The plasticity of epithelial lineage commitment and the ability of committed progeny to revert back to SCs may have important implications for tumorigenesis. In 1990, this notion was initially postulated by Bailleul *et al*., who observed that mice expressing an oncogenic *Hras* driven by a differentiation-specific promoter develop papillomas after wounding (92). In an interesting variation to this theme, normally fate-restricted, unipotent basal and luminal SCs of glandular epithelia reacquire certain features of multipotent SCs during tumor progression. For instance, tumor suppressor inactivation in luminal MG cells can lead to the formation of basal-like breast cancer (93), replete with heterogeneous expression of both basal and luminal markers.

Similar observations have been made for prostate cancer, where ablation of a tumor suppressor gene in luminal SCs induces tumor formation (57). Basal progenitors seem intrinsically more resistant to tumorigenesis, and even when they undergo a fate transition into luminal cells, the tumorigenic lesions that appear are less aggressive than those originating directly from luminal cells (56, 58).

Irrespective of underlying cause or mechanism, the plasticity within the tissue hierarchical organization is likely to have broader implications for tumor initiation and maintenance. In the intestine, for instance, adenomas arise from activating mutations in the Wnt/β-catenin pathway. After a single oncogenic hit, only *Lgr5/Bmi1/prominin*–expressing ISCs initiate tumor formation (39, 94, 95), whereas targeting TA progeny have either no effect or induce only microadenomas (94). However, concomitant activation of the Wnt pathway and another oncogenic hit cause normally committed TA cells to revert to a SC-like state and induce tumor formation (96).

Once initiated, these tumors may display hierarchical organization, replete with tumor-propagating cells (so-called cancer SCs), defined functionally by their ability upon serial transplantation to induce secondary tumors that resemble the parental tumor. Distinct populations of cells with tumor-propagating capacity capable of interconversion have also been identified within cancers (96–99), which raises the possibility that upon transplantation, more committed cells within a heterogeneous cancer may reacquire SC properties, analogous to the plasticity observed in normal SCs after transplantation. Consistent with this notion, non-SCs of human basal breast cancers can switch to SC state, depending on ZEB1, a regulator of the epithelial-mesenchymal transition (100). This result suggests a dynamic model where interconversion between low and high tumorigenic states can occur, which increases the potential for cancer progression. Further studies will be required to define the extent to which extent cell plasticity influences cancer growth and relapse after therapy.

Conclusion

The examples provided in this Review have highlighted the hierarchical and spatial organization of epithelial tissue homeostasis and the important plasticity of progenitors and differentiated cells during regenerative conditions. This cellular plasticity and lineage reversibility may represent adaptive mechanisms for the self-preservation of epithelia to repair body surfaces and linings in whatever ways possible after injuries. Across many different epithelia subjected to a diverse array of injuries, the paradigm emerging is that the minimum number of SCs needed to repair injuries will be activated and recruited during the healing process. As injuries become more severe, and greater numbers of SCs are depleted from their niches, more SCs become mobilized to participate in wound repair. When all SCs are exhausted, early progeny become recruited, until eventually, with massive injuries, the tissue can no longer cope with repair. Although the molecular mechanisms underlying cellular plasticity, fate conversion, and reacquisition of stem cell properties in committed and/or differentiated cells still remain poorly understood, these versatile built-in programs have major implications for regenerative medicine. On the flip side of this coin, however, is that when gone awry, these repertoires become the curse of epithelial SCs, most of which contribute in major ways to the most life-threatening of human cancers.

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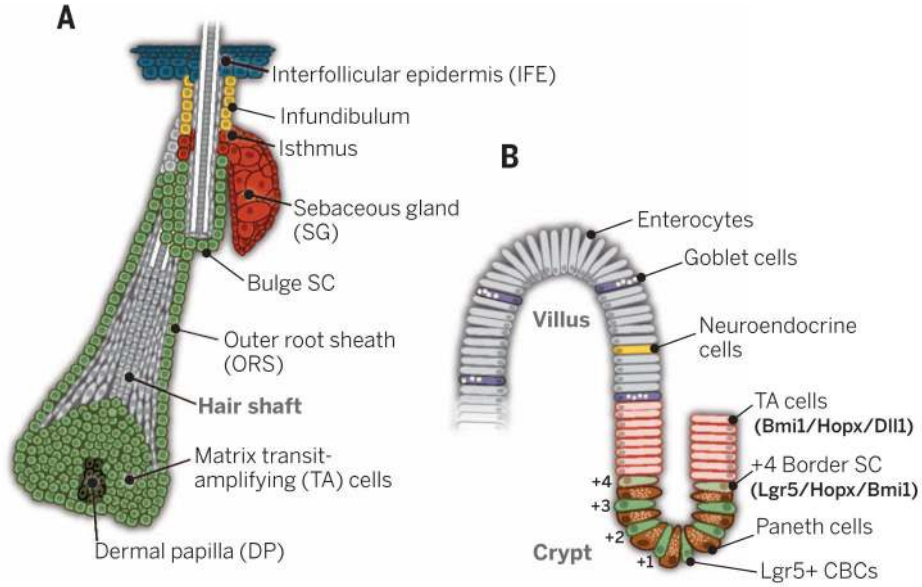

Fig. 1. Skin and intestinal epithelia: paradigms for epithelial stem cell biology

(**A**) Schematic illustrating the epithelial lineages of hairy skin, color-coded here, which derive from at least four distinct stem cell populations. (**B**) Schematic illustrating the location of intestinal crypt stem cells (green), giving rise to TA cells and, in turn, four distinct cell types, three in the villus and one in the crypt.

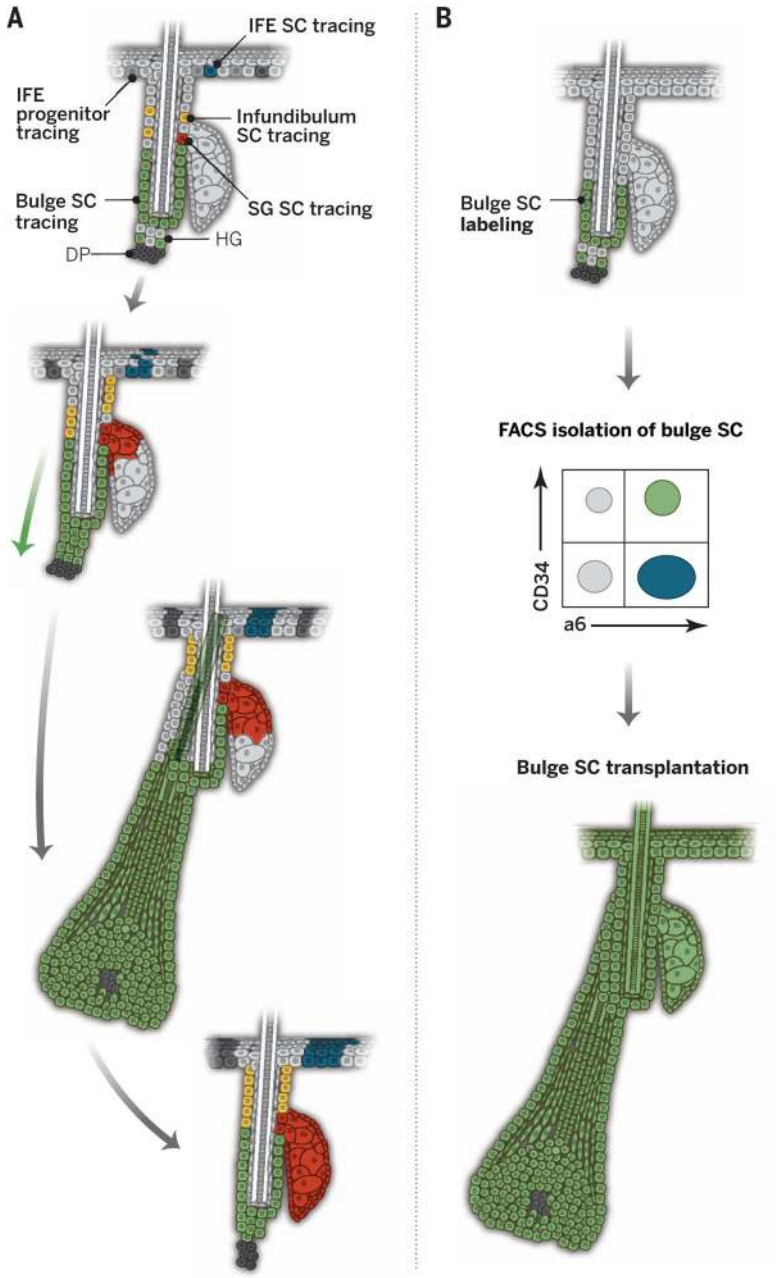

Fig. 2. Epidermal homeostasis is achieved through distinct pools of stem cells

(**A**) Schematic illustrating the outcome of five separate lineage tracings of Rosa26-floxed-stop-floxed–reporter mice. In each experiment, a different inducible Cre recombinase was expressed in the desired SC or progenitor compartment. Because the Rosa26 promoter is generic, once Cre is activated and the stop codon is excised, the marked cells and all their downstream progeny express the reporter. The results shown here illustrate that each SC compartment is responsible for sustaining tissue homeostasis within a discrete skin domain. (**B**) We purified fluorescently marked bulge SCs (green) by fluorescence activated cell sorting (FACS) and cultured them as individual colonies of cells before transplanting the

cells to a hairless mouse. The experiment illustrated that a clone from a single bulge SC can regenerate the entire skin epithelium, which documents the stemness and multipotency of the cells (9, 69, 70). We now know that when taken out of their native niche and engrafted, epithelial SCs are often less restricted in their fates.

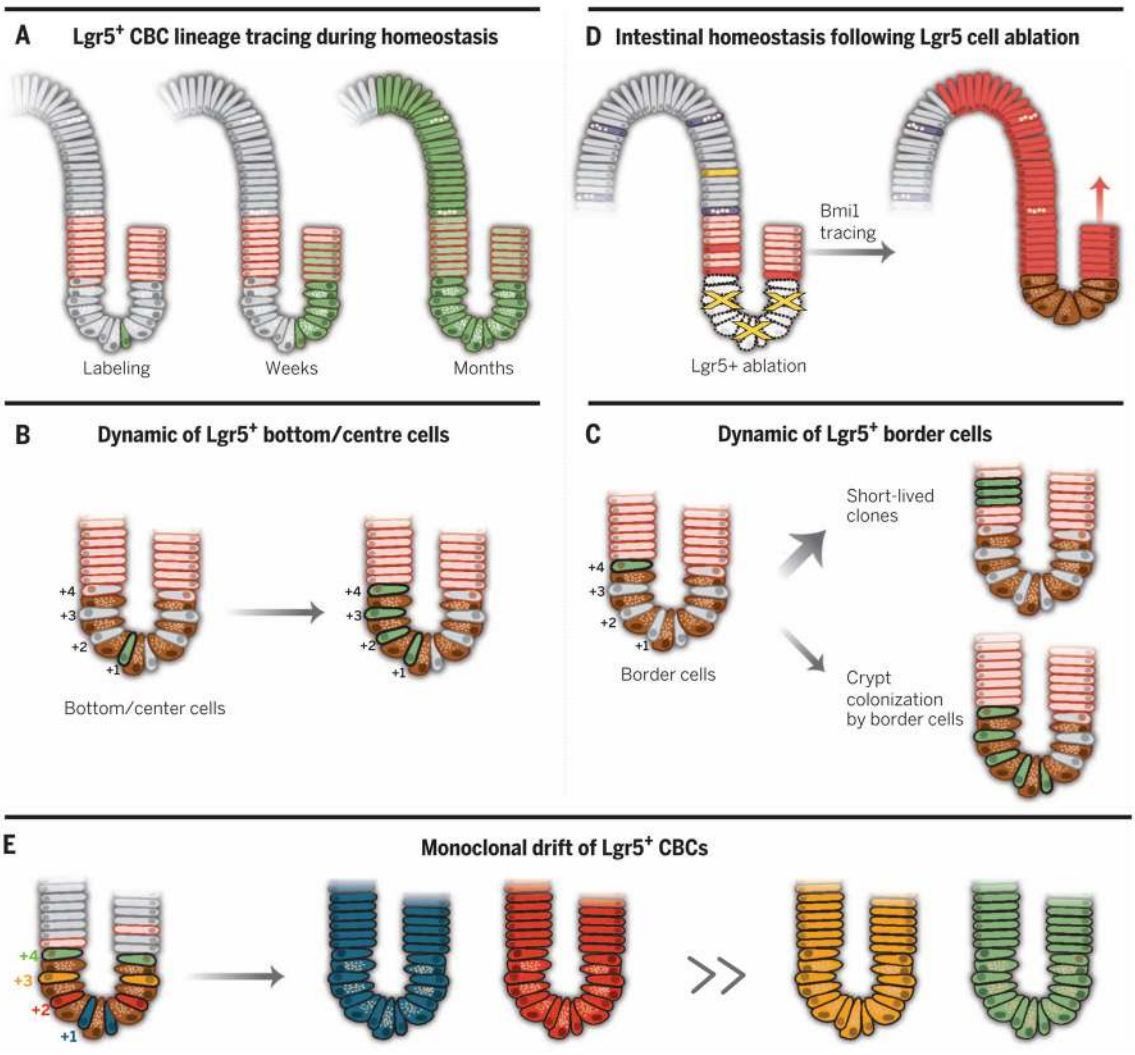

Fig. 3. Interconversion and monoclonal drift of intestinal stem cells

(**A**) Lineage tracing of *Lgr5*$^+$ cells (green) showing that these crypt cells give rise to all intestinal lineages during homeostasis (38). (**B** and **C**) Intravital microscopy showing the colonization of the crypt from *Lgr5* cells at bottom center. *Bmi1*$^+$ border (+4) cells either colonize the bottom of the crypt or give rise to TA cells (red) (42). (**D**) Lineage ablation of *Lgr5*$^+$ (yellow X's) prompts *Bmi1*$^+$ cells (red) to convert into *Lgr5*$^+$ crypt cells, and thus gut homeostasis is not impaired (43). (**E**) Multicolor lineage tracing rapidly leads to unicolor crypts, which demonstrate the monoclonal drift of ISCs (49).

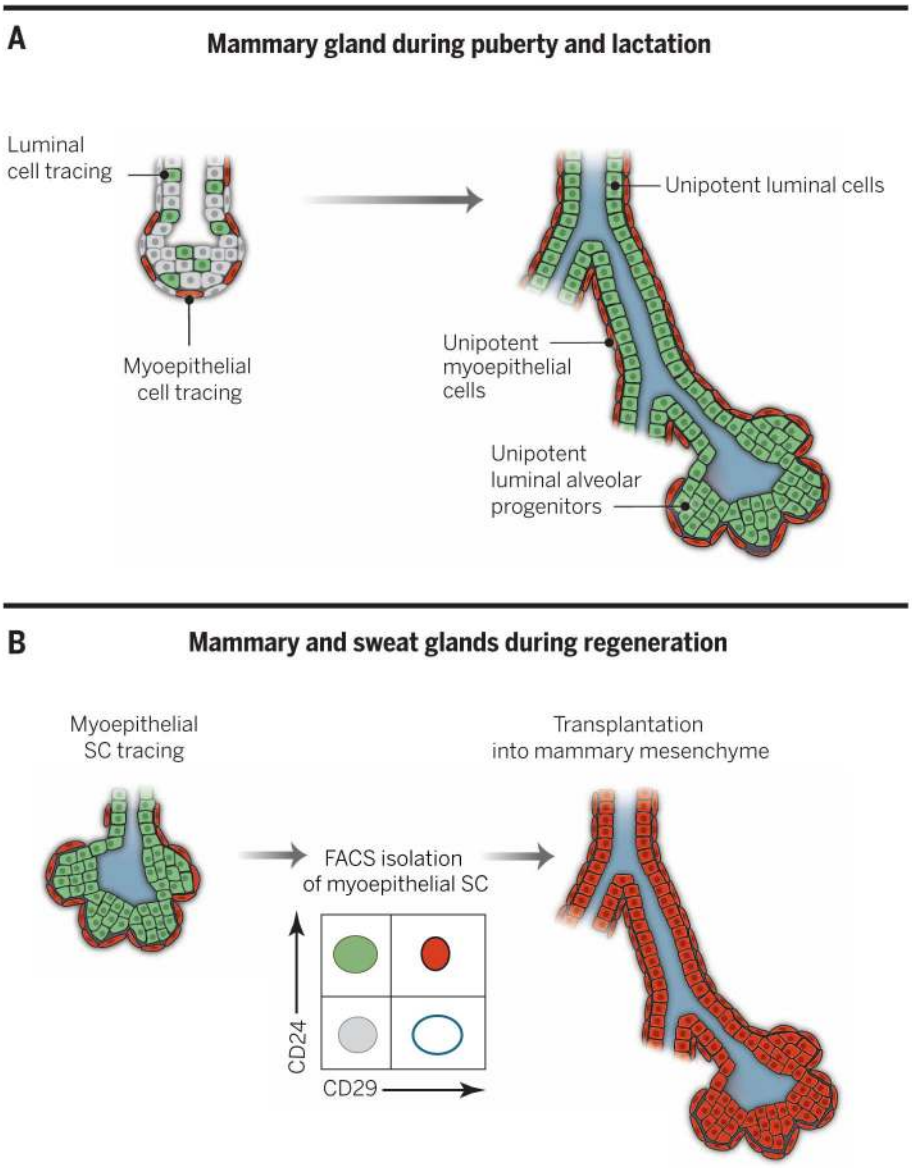

Fig. 4. Plasticity of glandular epithelium during regeneration

(**A**) Lineage tracing reveals that during puberty and pregnancy, MG expansion is sustained largely by unipotent myoepithelial cells (red) and luminal cells (green) (52). (**B**) After transplantation into mammary mesenchyme, unipotent myoepithelial cells (red) from the MG or the SwG acquire multipotency and reform a new gland replete with basal and luminal cells (52, 53).

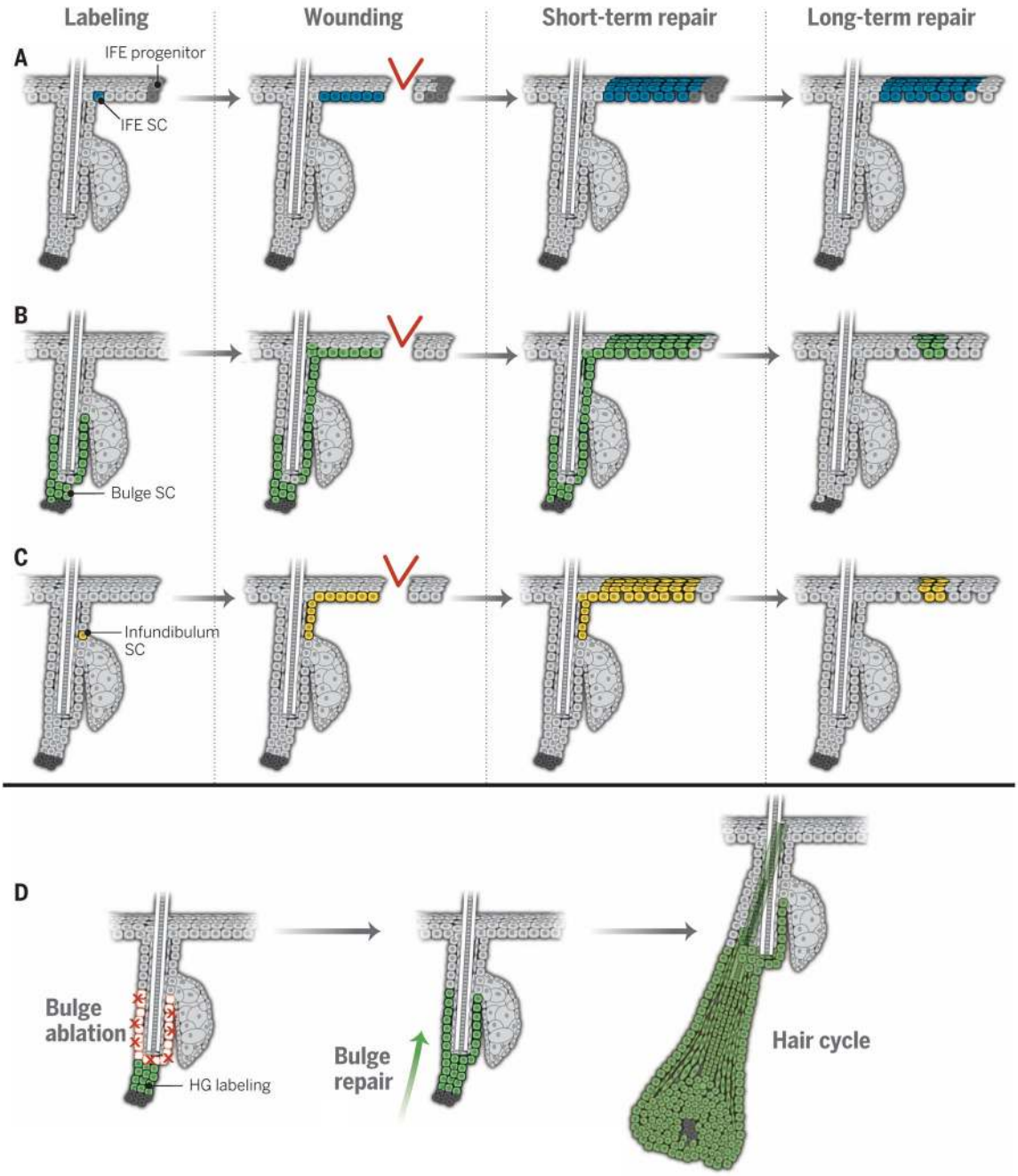

Fig. 5. Plasticity of epidermal cells during tissue repair

(**A**) Lineage tracing of IFE SCs (blue) and progenitors (grey) during wound healing showing that SCs stably contribute to epidermal repair while progenitor contribution is only transient (26). (**B** and **C**) Lineage tracing of bulge (B) and infundibulum SCs (C) demonstrate that adult HFSCs are rapidly recruited to IFE during wounding, but very few cells survive and contribute to IFE homeostasis after wound repair (19, 21). (**D**) After ablation of bulge cells (red X's), hair germ (HG) cells (green) recolonize the bulge niche and mediate hair regeneration (16).

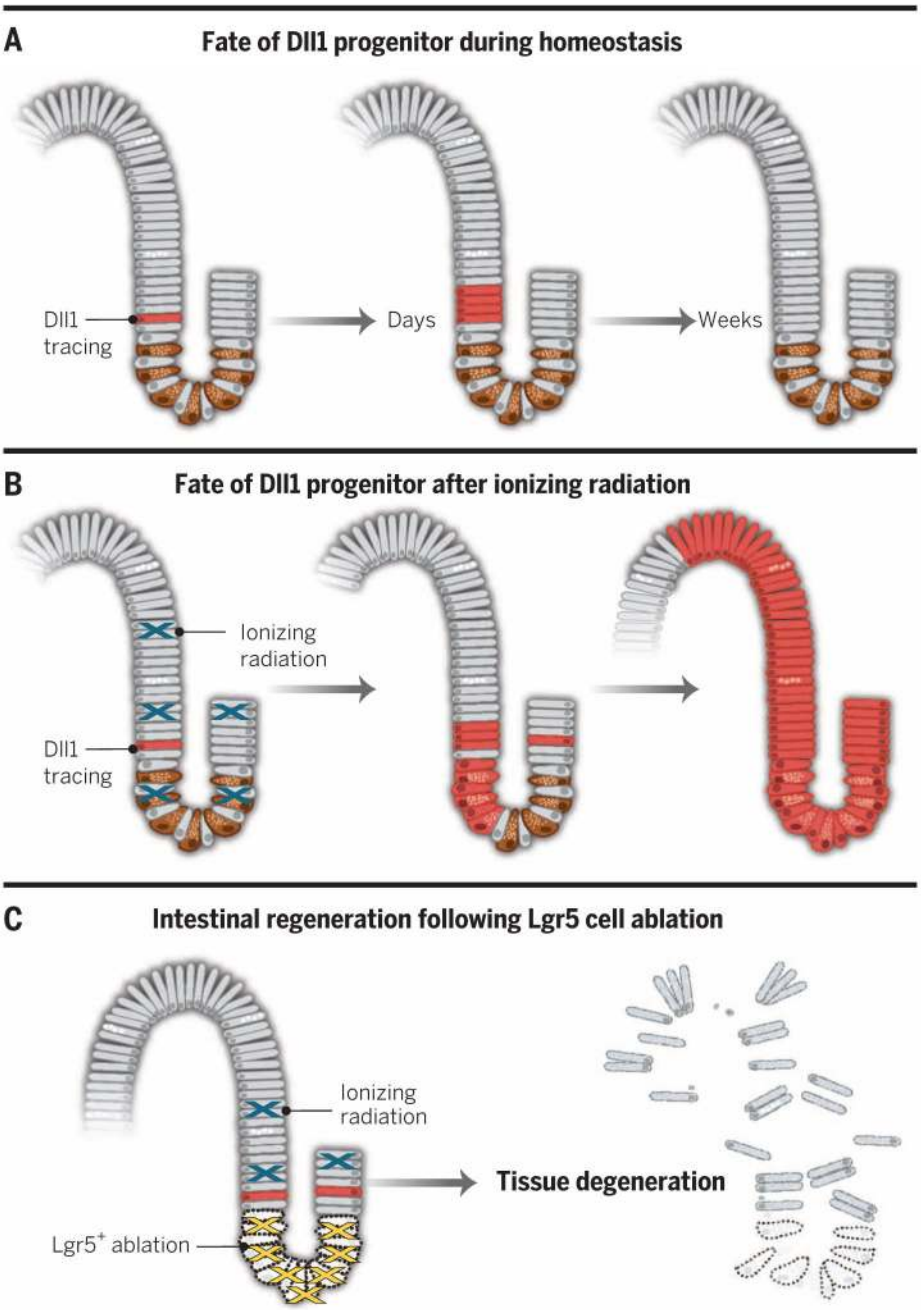

Fig. 6. Plasticity and interconversion into SCs during intestinal regeneration

(**A** and **B**) Dll1 lineage tracing showing that, although *Dll1*$^+$ cells (red) are transient and typically only differentiate into secretory cells (black; interspersed in villus) during homeostasis (A), upon γ-radiation–induced cell death (blue X's), *Dll1*$^+$ TA cells revert and colonize the crypt (B) (82). (**C**) When intestine is depleted of *Lgr5*$^+$ cells (yellow X's) and then exposed to γ-radiation, regeneration is impaired, revealing a critical role for Lgr5$^+$ cells in repairing extensive tissue damage (83).

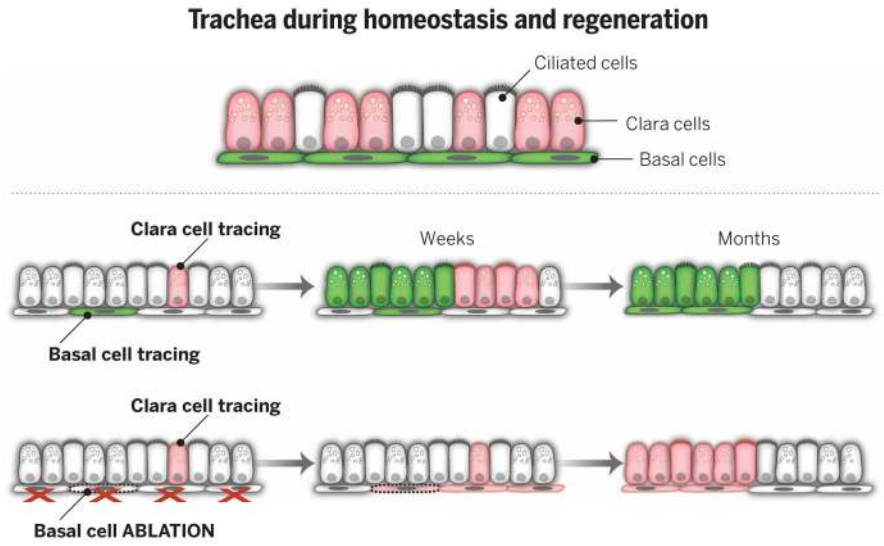

Fig. 7. Plasticity and interconversion into SCs during tracheal regeneration

During tracheal homeostasis, basal cells (green) give rise to TA Clara cells (pink) and terminally differentiated ciliated cells (white). Lineage ablation of basal cells (red X's) induces the interconversion of Clara and/or ciliated cells into basal SCs (85).