Supplementary Note

Clonal dynamics of the back skin IFE

To address the changes in cell fate that accompany stretch-mediated expansion of mouse back skin interfollicular epidermis (IFE), it is necessary to first establish a model of the unperturbed system based on the quantitative analysis of the clonal data. To record the total output of individual labelled cells, clones were scored based on the number of basal and suprabasal cells. Since the K14 promoter can in principle target all basal cells, whether proliferative or terminally differentiated, we focused on the ensemble of clones that retain at least one basal cell (Fig. 2a-c and Extended Data Fig. 4a, b). By focusing on the population of "persisting" clones, we circumvent the challenge of trying to identify single-cell clones that had already terminally differentiated at the time of induction, as well as mitigating potential uncertainties surrounding the relative efficiency of the K14 promoter in labelling proliferative and differentiated basal cell populations. Although this approach also neglects the transient population of expanded clones that have fully-differentiated, stratified, but not yet become fully shed, the joint distribution of basal and total size of persisting clones provides an rich data set that can be used to constrain any viable model.

To confirm that the K14 promoter targets cells that include the self-renewing basal cell population, we first determined the time-evolution of the average labelled cell fraction, obtained as the product of the average basal clone size and the areal density of persisting clones (Fig. 2d-f). In homeostasis, the average labelled cell fraction must converge over time to a constant value, with any transient variation being a measure of the degree to which the K14 promoter targets preferentially the self-renewing population[1]. Despite potential mouse-to-mouse variation in the induction efficiency, the average labelled cell fraction of the control system remained approximately constant over the two-week time course (Fig. 2e), indicating that clonally labelled cells include the renewing basal cell population.

Next, we considered whether features of the clonal data could provide insight into the fate behaviour of individual cells. Previously, it has been shown that, for stem cell renewal strategies of epithelial maintenance based on population asymmetry, where stochastic stem cell loss through differentiation is compensated by the duplication of neighbours, the distribution of clone sizes converges over time to a statistical scaling behaviour characterised by an exponential size dependence[2]. Consistently, and in common with the behaviour reported in other mouse epithelial tissues, analysis of the basal and total clone size distribution of the back skin IFE at the longest time point, day (D)14, revealed an approximate exponential dependence (Fig. 2h), consistent with population asymmetric self-renewal.

Early clonal tracing studies of mouse tail epidermis placed emphasis on a model in which IFE is maintained by a single equipotent population of basal progenitors where the frequencies of stochastic cell duplication and terminal division are balanced so that, on average, their number is maintained constant over time – a dynamics known as a "critical birth-death" process[3]. (For an up-to-date review of this original "one-progenitor cell model" and its application to a range of clonal fate studies, see Ref. [4].) However, based on the statistical scaling behaviour of clone sizes alone, more "refined" models of cell fate cannot be ruled

out[2]. In particular, a hierarchical organization in which commitment to differentiation occurs not directly, but through a limited series of terminal divisions would, in the long-term, give rise to the same exponential dependence of the clone size distribution. Moreover, in the planar two-dimensional geometry of the IFE, exponential scaling behaviour of the size distribution cannot discriminate between models in which fate asymmetry is regulated through a cell-autonomous programme, or one in which cell duplication and differentiation are locally correlated in space, i.e. stochastic cell division follows in response to the differentiation and delamination of a neighbour, or *vice versa*[2]. It is, however, clear that, in the 2D setting of the skin epidermis, a *purely* cell-intrinsic programme would not be tenable over the long-term[5].

However, by studying detailed features of the clone size distribution at shorter chase times (prior to the onset of scaling), further insight into potential heterogeneities and fate of basal progenitors can be sought[6]. Notably, in the current study, inspection of the basal clone size distribution revealed evidence of a small but statistically significant bias towards clones containing an even number of basal cells: Across the two-week time course, some 65±5% of persisting clones have an even number of cells (Fig. 2b and Extended Data Fig. 4c), a correlation that remained visible in the total clone size distribution. In principle, such a feature might have been (and in earlier studies was) attributed to statistical fluctuations due to small clone number statistics, or transient effects created by synchronicity in the timing of cell division and/or stratification. However, significantly, this even-odd correlation of clone size remained pronounced even at longer chase times and for larger clone sizes, and became dramatically enhanced under perturbed conditions (see below), suggesting that its origin may provide a signature of the underlying cell fate behaviour.

One-progenitor model

Based on previous studies, we first considered whether the even/odd signature could be explained within the framework of a one-progenitor model, hypothesizing that its origin could lie in a predominance of cell divisions leading to symmetrical fate outcomes. To test this idea, we first considered a minimal two-dimensional (square) lattice model in which each site plays host to precisely one basal and one suprabasal cell, consistent with the relative cell fractions observed in steady-state. Then, with probability $1-r$, cell division leads to asymmetric fate outcome, with one cell remaining in the basal layer and the other transferring to the suprabasal cell layer. Conversely, with probability r, cell division results in correlated symmetric fate outcome, where one daughter cell remains on the original site and the other “displaces” the cell at a neighbouring site, leading to its differentiation and stratification (Fig. 2l, left). Conceptually, we may think of such a replacement event as a reflection of a prior symmetric terminal division of the neighbouring renewing cell during its previous round of division. In the particular case that $r=1$, such behaviour translates to the “Voter model” dynamics proposed famously by Marques-Pereira and LeBlond in studies of rat oesophagus[7] and, developed more recently, by Mesa et al. in the context of the mouse ear epidermis[8]. In this case, the dynamics involves only symmetric fate outcomes – correlated symmetric duplication and terminal division. In the general case, where $r<1$, the model allows for a degree of fate asymmetry.

To fit the model to the data, we made use of a least-squares fit of the marginal distribution of basal and total clone size to the results of stochastic simulation (based on the analysis of an ensemble of 10^6 units organized in a square lattice), taking as an initial condition individually labelled cells in the renewing basal compartment at "day -3". Scanning the two-dimensional space of parameter values, we computed the mean-square difference between the result of the model simulation and the distribution of basal and total clone sizes, integrated across all time points. Based on this analysis, we obtained the best fit (least-square value) for $r = 0.72$ and a cell division time of $1/\lambda = 4.8$ days (Extended Data Fig. 3i-m). The map of least-square values (Extended Data Fig. 3l) shows the sensitivity of the model fit to the data. Notably, despite a tilt towards symmetric fate decisions (viz. $r > 0.5$), the fits did not reproduce "even-odd" correlations in clone size (Extended Data Fig. 3m). Based on such a one-progenitor model, the irregular timing of cell division, combined with the stochastic stratification of differentiating cells out of the basal layer and their subsequent loss from the tissue, leads to a rapid erasure of even-odd correlations.

Similarly, we considered whether local spatial fluctuations in cell density could lead to correlated cell division or delamination, i.e. if the local cell density were high, the two daughter progenies of a basal cell division might be more likely to differentiate and delaminate while, if the local density were low, the progeny might be more likely to remain in the proliferative compartment[9]. However, we reasoned that, although such local density fluctuations might lead to transient pair correlations in the clonal data, if any pair of neighbouring cells could participate equally in progenitor cell loss and replacement, such effects would, once again, become rapidly erased from the clonal record. The persistence of even-odd correlations to longer time points (Fig. 2b and Extended Data Fig. 3c) and, indeed, its re-emergence as an even more prominent feature in perturbed conditions (discussed below), suggested that its origin must instead be rooted in a persistent niche-like organization.

Two-progenitor model

To this end, we next considered an organization that echoes the canonical epidermal proliferative unit (EPU) paradigm[10, 11]. Specifically, we hypothesized that the back skin IFE is comprised of a mosaic of units, each of which plays host to precisely two basal cells and their differentiated suprabasal cell progenies. Then, in the course of tissue turnover, the differentiation and stratification of a basal cell is compensated by the division of its partner within the same unit. Indeed, such a model of basal cell loss compensated by local cell division would mirror the Voter model considered above. However, to account for the prevalence and persistence of even cell numbers in clones, we reasoned that cell differentiation must involve a terminal division so that not one, but two differentiated cells enter the suprabasal cell layers. Within such a framework, following the random genetic labelling of basal cells, individual clones would either become quickly lost through terminal division and stratification, or the unit would become "monoclonally fixed" with both basal cells in the unit labelled and, depending on the nature of cell loss (viz. shedding), suprabasal cells numbers also enriched for even values.

Although such a model would capture (trivially) the even-odd character of the data, persisting clones do not become "fixed" with just two basal cells, but continue to expand in

141 size over time while others are lost through differentiation, calling for a further refinement
142 of the "proliferative unit" model. Therefore, we further proposed that such a pattern of
143 correlated cell loss and replacement can occur (see Fig. 2l, right for details), albeit at a
144 potentially reduced frequency, between neighbouring units as well as within units. In this
145 case, the unit structure would ensure enrichment of even clone sizes while, over the long-
146 term, the envelope of the clone size distribution would converge onto the hallmark
147 exponential scaling form implied by such a pattern of correlated stochastic progenitor cell
148 loss and replacement between neighbouring units.
149
150 Lastly, to complete the definition of the model, it was necessary to define whether both
151 basal cells within an individual unit have the same renewal potential, or whether they are
152 arranged in a hierarchy with one cell harbouring long-term renewal potential and the other
153 irreversibly committed to differentiation via terminal division. Notably, analysis of all clones
154 (persisting and "basal-detached") at the D2 time point – which translates to some 5 days
155 post-induction – showed that the vast majority of 2-cell clones (80 out of 101) were
156 restricted to the basal layer (Extended Data Table 1), suggesting that the K14 promoter
157 targets cells primed for renewal. Moreover, of the remaining 21 two-cell clones, just 4
158 comprised one basal and one suprabasal cell, while the majority comprised two suprabasal
159 cells, consistent with terminal division and correlated stratification of sister cells. Finally,
160 among the small minority of clones containing a total of 4 cells, 5 were all basal, 2
161 comprised a basal pair and a suprabasal pair, and 1 was fully-suprabasal. No 4-cell clone
162 contained an odd number of suprabasal cells. Taken together, these results were suggestive
163 of an engrained hierarchy within the units, with one basal cell belonging to the renewing
164 compartment and the other committed to differentiation through terminal division.
165
166 Before considering what might be the basis of such a two-progenitor compartment model,
167 its specificity, and its relation to previous models of IFE maintenance, we first considered
168 the extent to which it could capture the clonal dynamics of the homeostatic control system.
169 To this end, we considered a two-dimensional square lattice of units, each of which hosts
170 one renewing basal progenitor (which we termed a "stem cell"), and one basal progenitor
171 committed to differentiation through one round of terminal division and stratification (Fig
172 2l, right). (Note that variations in the coordination number of the lattice – square vs.
173 hexagonal, etc. – would lead to only minor changes in the predicted clone size distributions
174 whose effects would in any case be beyond the resolution of the experimental data.) Then,
175 at rate λ, basal cells divide so that, with probability $1-r$, the renewing basal cell undergoes
176 an "asymmetric division" replacing its partner in the same unit which, in turn, undergoes
177 terminal division and stratification into the suprabasal layer. Here, for simplicity, we
178 suppose that terminal division and stratification occur contemporaneously so that the two
179 differentiated daughter cells are transferred immediately to the suprabasal cell layer. A
180 generalization of the model that allowed for a small time delay between terminal division
181 and stratification would not significantly alter the predicted clonal dynamics, providing that
182 stratification of sister cells occurs in a near-synchronous manner – a correlation consistent
183 with the D2 clonal data (Extended Data Table 1) and, in fact, reported in the live-imaging
184 study of ear epidermis[12]. Conversely, with probability r, the renewing basal cell divides
185 symmetrically, replacing a "renewing" basal cell in a neighbouring unit, which in turn
186 undergoes terminal division and stratification.
187

Finally, to accommodate the loss of suprabasal cells through shedding, we proposed that the production of new differentiated cells within a given unit leads to the displacement and irreversible loss of existing suprabasal cells in that unit. To accommodate the effects of stochasticity in the loss rate, we considered a suprabasal capacity that is twice the measured value, but randomly reject one half of the cell pairs in scoring the total suprabasal unit occupancy of cells. (Note that, since stem cell loss-replacement events involve the correlated cell division of two renewing stem cells, the average cell cycle time, τ, of renewing cells is related to λ through the relation $\tau = (1-r)/\lambda + 2r/\lambda = (1+r)/\lambda$. Moreover, since the composition of each unit is balanced, the division rates of the renewing and committed cells must be equal.) In summary, in steady-state, the model depends on just two adjustable parameters, λ and r, which must be fit against the range of basal and total clone size data, integrated across multiple time points (Extended Data Fig. 4a).

Scanning the two-dimensional space of parameter values (Extended Data Fig. 3n), using a least-square fit, we obtained the best fit with $1/\lambda = 4.5$ days and a relative rate of symmetric division of $r = 0.21$, i.e. some 4 out of 5 renewing basal cell divisions result in asymmetric fate outcome within a unit, while 1 in 5 result in the loss and replacement of a neighbour – values that resonate with reported fits to the one-progenitor model in other epithelial contexts[3,4,13]. With this parameter combination, the marginal clone size distributions reproduced the hallmark even-odd signature and an excellent fit to the measured clone size distributions (Extended Data Fig. 4a). The same parameter choice faithfully predicted the average clone size dependences and clonal persistence (Fig. 2c, d)

Based on this analysis, we found that a minimal (two-parameter) two-progenitor model is capable of predicting the range of clonal data. However, generalizations and refinements of the model in which, for example, progenitors are capable of more than one round of terminal division, a time-delay is introduced between terminal division and stratification, progenitors and stem cells are capable of a low rate of interconversion, etc., cannot be ruled out. In this sense, the current model should be considered a caricature of what may be a richer, more complex, cellular organization and dynamics. However, we can conclude that a model based on an equipotent one-progenitor cell model is not consistent with the fine even-odd signature of the short- and long-term clonal data in the back skin IFE. While the application of the model to other epithelial tissues lies beyond the scope of the current study, it is interesting to note that a similar persistent even-odd signature in clone fate data is clearly visible in the mouse oesophagus, even after 6 months tracing post-induction (see Fig. S4c of Ref.[4]) suggesting that such a hierarchical organisation may in fact be a conserved feature of squamous epithelial tissues.

At its core, the proposed model shares much in common with the model of Marques-Pereira and LeBlond[7]. In this paradigm, the basal layer constitutes an open or "facultative" niche in which chance differentiation and stratification of basal keratinocytes is compensated by the symmetric division of a neighbour. This scenario has received renewed interest through intravital live-imaging studies of the mouse ear epidermis by Mesa et al.[8], backed up by functional analyses of biomechanical signalling by Miroshnikova et al.[14]. From the quantitative analysis of short-term cell dynamics and the spatial reorganization of basal cells following cell delamination, a model was proposed in which stratification drives symmetrical division of neighbours. In this model, cell fate is not assigned during division, but through

sporadic differentiation linked to cell stratification. In the current model, cell delamination is also correlated with cell division, but differentiation occurs through one round of terminal division. Importantly, by decoupling commitment to differentiation from cell delamination, these findings suggest that stem cell fate is assigned during cell division within the basal layer raising the question of how fate balance is regulated mechanistically.

Is there a precedent for the current two-progenitor compartment model? Indeed, the proposed cellular organization is reminiscent of that inferred from the clonal analysis of the *Drosophila* midgut[15]. Here, stem cells lie anchored tightly to the basement membrane, giving rise to enteroblasts that mature into enteroendocrine cells or, through endo-replication, into enterocytes. In the course of turnover, stem cells predominantly undergo asymmetric divisions, replenishing cells within their “unit” (or “nest”) while, with lower probability, symmetric division leads to the stochastic loss and replacement of stem cells at neighbouring sites. In this case, intestinal stem cells compete neutrally for territory on the basement membrane while giving rise predominantly through asymmetric division to progenies that are committed to a differentiation pathway that, in this case, is not accompanied by cell division.

Clonal dynamics during TPA treatment

Before considering whether the two-progenitor cell model can capture the clonal dynamics during stretch-mediated expansion of tissue, we first turned to consider the role of TPA treatment. Although TPA administration may elicit an additional stress response, from the perspective of the clonal dynamics, prolonged treatment is expected to establish a new steady-state that, from the BrdU incorporation data (Extended Data Fig. 4d-f), involves an overall increase in the basal cell division rate by a factor of around 2. Consistent with this increase, analysis of the clonal data shows a corresponding increase in the average clone size, while the predominance of clones bearing an even cell number becomes extremely pronounced (Extended Data Fig. 4g). Focusing on D1 and D14 time points, we therefore questioned whether the basal and total clone size distribution could be predicted using the same model as the control, but with an elevated division rate. From a least-squares analysis, we found the two-progenitor cell model could provide an excellent fit to the clonal data with an average cell division time of $1/\lambda = 2.8$ days, an increase quantitatively consistent with the BrdU data, and $r = 0.14$, decreased from that found under unperturbed conditions (Extended Data Fig. 4e). Notably, with this reduction in the frequency of loss/replacement events, the model faithfully reproduced the pronounced even-odd signature in basal and total clone sizes. In this case, since the one-progenitor model cannot recapitulate an even-odd signature, its quantitative comparison was not considered.

Clonal dynamics during stretch-mediated expansion

With these preliminaries, it was now possible to address the clonal dynamics following stretch-mediated expansion. Specifically, following the same induction protocol as used for control animals, at day 0 the tissue was subject to an abrupt isotropic expansion that was accommodated initially through a corresponding increase of the basal cell surface area leading to a proportionate decrease in cell density. This perturbation in cell density then became progressively resolved through excess cell proliferation in the basal layer (Fig. 1b-e).

282 This adjustment in cell kinetics and fate was reflected in a strong perturbation of the clone
283 size dependences, recorded over the two weeks chase (Fig. 2g-j).
284
285 In common with the control data, the distribution of basal clone sizes also showed
286 convergence towards an exponential dependence (Fig. 2k) characterised by a single size
287 scale, suggesting that the expansion of tissue is likely to be mediated by a single equipotent
288 population. However, in this case, the expansion in average basal clone size was not
289 compensated by a drop in clone persistence, consistent with the net number of marked
290 basal cells increasing overall, as expected during the expansion of tissue (Fig. 2i). Moreover,
291 the estimate of clone persistence showed no statistically significant change between 2 and 4
292 days post-expansion, consistent with clones being approximately conserved in number over
293 the early phase of recovery.
294
295 Although the distribution of clone sizes preserves the exponential dependence, this does
296 not mean that the underlying fate behaviour and proliferation kinetics must be invariant
297 during and after the period of expansion. Indeed, measurements based on BrdU
298 incorporation suggest a dramatic adjustment in the cell cycle rate, changing by more than a
299 factor of 2 following expansion, before subsiding towards the normal steady-state value by
300 around D14 (Fig. 1e). At the same time, there was a significant, and relatively abrupt,
301 thickening of the IFE following expansion, translating to an increase in the number of
302 suprabasal cell layers from around one to four (Fig. 1f,g).
303
304 To model the dynamics during stretch-mediated expansion, we looked for a minimal
305 adjustment of the steady-state model, taking as an input the measured variation in the
306 basal cell proliferation rate, as inferred from BrdU incorporation, normalised by the control
307 estimate of the average cell proliferation rate. Following expansion, the area of IFE is
308 increased by a factor of around 2 (Fig. 1a-c). To accommodate this increase, we
309 implemented the following "computational trick": First, to seed the lattice simulations with
310 the initial clone size distribution at the time of expansion, we allowed the system to develop
311 in the manner of the control group over the first 3 days post-induction. Then, on expansion
312 (defined as day 0), we "emptied" at random precisely one half of cell lattice sites (basal and
313 suprabasal), mimicking the associated reduction in cell density by a factor of two following
314 stretch-mediated expansion. Then, we allowed renewing basal cells to repopulate the lattice
315 sites through symmetrical division, leading to the repopulation of unoccupied sites. Such a
316 programme can be captured by the same intra- and inter-unit cell division processes as in
317 the steady-state control condition, but without the requirement that basal cell duplication
318 be compensated by terminal division and stratification of neighbours; rather, compensation
319 would only occur if target sites were already occupied, as in steady-state. Such dynamics
320 would then lead to a progressive regeneration of tissue back towards steady-state, even if
321 the net basal cell division rate, λ, and the relative rates of symmetric and asymmetric
322 division, r, were left unchanged from their steady-state values. However, based on BrdU
323 incorporation measurements, we know that the division rate changes significantly over the
324 early time course, and we can anticipate that the fate parameter, r, is also changed in
325 response to the perturbation, reflecting the need to expand the basal progenitor pool. In
326 principle, this engages a "continuum" of fit parameters, indexed by the temporal variation
327 of r, alongside potential further fine-tuning of the division rates. However, in practice, the
328 division rates are heavily constrained by the BrdU assay, leaving only the associated r values

between the respective four chase time points as effective fitting parameters, limiting significantly the available phase space for model fitting.

Applying this minimal model, we obtained a remarkably close fit to the data, faithfully reproducing much of the fine detail in respect of the even-odd clone size variation, and its enrichment at the longest chase times (Fig. 2g, Extended Data Fig. 3h and Extended Data Fig. 4b-d). Based on a coverage of the parameter space of r values, a least-squares fit of the model to the marginal basal and total clone size distributions showed that the abrupt increase observed in the division rate (Extended Data Fig. 4b) is accompanied by a parallel pulse increase in r following expansion (Extended Data Fig. 4c), which subsides dramatically, falling almost to zero at the two longest chase times.

Finally, the observed increase in average clone size does not straightforwardly translate to a corresponding overall increase in suprabasal cell number over the time course. On this basis, it seems likely that the increase in suprabasal cell number is achieved through the retention of some differentiated cells following expansion rather than an overt increase in the production rate of newly-differentiated cells as a proportion of the progenitors, a conclusion supported by detailed measurements of all clones (including fully basal-detached) at EXPD2 (Extended Data Table 2).

Expansion during treatment conditions

Lastly, to complete our analysis of the clonal data, we considered the behaviour under two treatment conditions: the inhibition of MEK/ERK/AP1 pathway by Trametinib and the MAL inhibitor. For details of the predicted effects of the inhibitors, we refer to the main text. Despite the scale of the perturbation imposed by the hydrogel, in treated conditions, analysis of BrdU incorporation showed that the abrupt area increase resulted in only a modest and sustained increase in the cell proliferation rate (Fig. 4f and Extended Data Fig. 10d). Therefore, to analyse the data, we considered the two-progenitor compartment model in which, following expansion, the average cell division rate, λ, and degree of asymmetry, r, were adjusted to values that remained constant over the short time course of the experiment.

Applied to the TRAM treatment, we found that the fine structure of the basal and total clone size could be reproduced with an average cell division time, $1/\lambda = 4.3$ days, a reduction quantitatively consistent with the BrdU data, and $r = 0.17$, decreased from that found under unperturbed conditions (Extended Data Fig.12b, e, f). Similarly, for SRF treatment, we obtained an excellent fit to the clonal data with an average cell division time, $1/\lambda = 3.8$ days, consistent with the BrdU data, and $r = 0.08$ (Extended Data Fig.12a, c, d). These results show that, under SRF treatment conditions, and to a much lesser extend in the TRAM treatment, the fraction of stem cell divisions resulting in symmetric renewal is strongly decreased, providing a striking contrast with the untreated expansion conditions.

Discussion

In defining the cellular basis of epidermal fate, our aim was to find the simplest model that is consistent with the wide range of clone fate data across all conditions. Given the rapid

376 convergence of the clone size distribution to an exponential-like scaling dependence, a
377 feature found ubiquitously in clonal lineage tracing studies of epithelial tissues[4], we
378 imposed the constraint that the model must have at its apex an equipotent self-renewing
379 cell population that is stochastically lost and replaced[2]. However, such scaling behaviour
380 cannot rule out the existence of a more complex hierarchical cellular organization[2]. Here,
381 we have used finer-features of the clonal data to identify and characterize heterogeneity
382 with the proliferative compartment. Using this approach, we found that a persistent
383 even/odd signature in the clone size data provided evidence for a proliferative hierarchy in
384 which stem cell differentiation is not direct, but occurs through one round of terminal
385 division. Moreover, to sustain robust even/odd correlations over the long-term, we found
386 evidence of a local niche-like organization in which progenitor cell loss through terminal
387 division must be compensated predominantly by the asymmetric division of the *same*
388 neighbouring stem cell. Whether this association is communicated by environmental signals
389 from the extracellular matrix, polarity cues, or other environmental factors remains an
390 important and interesting open question. Alongside clonal fate data, further evidence for
391 proliferative heterogeneity was found from the analysis of scRNA-seq data.
392
393 Finally, although the two-progenitor cell model is able to predict the clonal dynamics across
394 a range of conditions, more complex models involving further sub-compartmentalisation of
395 the proliferative compartment cannot be ruled out. Equally, further studies will be required
396 to assess whether the same cellular organization prevails in other squamous epithelial tissue
397 types. Importantly, this model will be important in identifying possible biochemical and
398 mechanical mechanisms that regulate basal cell fate choice.
399
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402

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