Cell

A Collective Path toward Regeneration

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How do cells collectively control an organ's behavior? By plucking various numbers of hairs from the mouse skin, Chen et al. show that hairs regenerate only when a sufficiently high density of them are plucked. Remarkably, a hair follicle can only regenerate in concert with other follicles, but not autonomously.

A cell can modify its behavior in response to signaling molecules secreted by its neighboring cells. This cell, in turn, can secrete a signaling molecule that changes its neighboring cells' behaviors. In a population of cells, such a dynamic back and forth between many cells means that there are often no sharp boundaries between actions of cells that are autonomous and those that influence other cells. This blending of many individuals into one collective entity, often at a macroscopic scale, is a hallmark of multicellular systems like tissues, organs, and populations of bacteria. It also necessitates quantitative analyses to identify the cascades of events that yield collective behaviors of cells. In this issue of *Cell*, Chen et al. (2015) use mathematical models and experiments to reveal that a group of hair follicles can "count" how many hairs have been plucked from the skin and then regenerate the lost hairs if the density of plucked hairs is above a certain density (i.e., "threshold density") while not regenerating any hairs if the density of plucked hairs is below this threshold density (Figure 1A). The authors have thus uncovered a rare example of quorum sensing, which has mainly been studied in bacteria, at the level of a whole organ in a live animal.

Chen et al. (2015) studied hairs that grow on the mouse skin. A "hair unit" consists of a hair that protrudes from the skin and its follicle that lies beneath the skin (Figure 1A) (Jahoda and Christiano, 2011). The follicle contains the stem cells from which a new hair can grow. The authors counted and plucked individual hairs from mice. By varying the geometry of regions on the skin from which the hairs were plucked and the number of plucked hairs, the authors discovered two scenarios. When the density of plucked hairs was below a certain threshold density, no follicles regenerated (Figure 1A). But when the density of plucked hairs was above the threshold density, both the follicles of the plucked hairs and of the surrounding intact hairs regenerated (Figure 1A). Thus, hair follicles are not autonomous. Instead, they collectively decide whether or not to regenerate both the lost and intact hair follicles. This ability of the follicles to measure the density of lost hairs is a form of quorum sensing (Ng and Bassler, 2009), in which a group of cells "measure" its population density and then together launch a collective action (i.e., regeneration of all hairs) only when the density is high enough. Using quorum sensing, the follicles can ignore harmless minor hair losses while using its resources to repair only harmful major hair losses.

Remarkably, Chen et al. (2015) discovered that a field of hair follicles spanning macroscopic distances (i.e., several mm) could quorum sense. Before degrading or being captured by a cell, a typical signaling molecule can travel no more than about 100 μm. Thus, a "distressed" follicle (i.e., a follicle of a plucked hair) can potentially use a signaling molecule to tell its adjacent follicle, which is typically about 100 μm away, of its hair loss. However, using a mathematical model, the authors deduced that follicles could not quorum sense across millimeter distances if they could only communicate with their immediate neighbors. In fact, they found that follicles must secrete a signal that traveled over a distance of 1 mm, at a higher speed than any molecule could achieve. Turning back to the bench, the authors discovered that a distressed follicle recruited M1 macrophages to it by secreting the attractant chemokine CCL2 (Figure 1B). Immunostaining revealed that these motile macrophages first accumulated around the distressed follicles and then around the surrounding healthy ones. The macrophages secreted the signaling molecule Tnf-α that stimulated the regeneration of both the healthy and distressed follicles through pathways that remain to be uncovered (Figure 1B). Although more work is required, the authors' data suggest that an appreciable accumulation of macrophages around the distressed follicles most likely occurs only when the density of distressed follicles is above the threshold density (Figure 1C). More importantly, the authors show that motile cells, along with signaling molecules, can transmit information over a macroscopic distance between immobile cells. An interesting question for the future is if such coupling between random diffusion of signaling molecules and directed motion of signaling cells may underlie collective behaviors of other organs.

An unresolved mystery is what determines the threshold density of hair loss. In microbial cells, the threshold that divides whether every cell or no cell responds to a signaling molecule is primarily determined by the binding affinity of the molecule to its receptor and a positive feedback regulation in a genetic circuit that controls the cells' response to the signaling molecule (Ng and Bassler, 2009; Pai et al., 2014; De Monte et al., 2007; Rotem et al., 2010). But, in multicellular systems, it is unclear how coordination of many different factors leads to a threshold and a binary

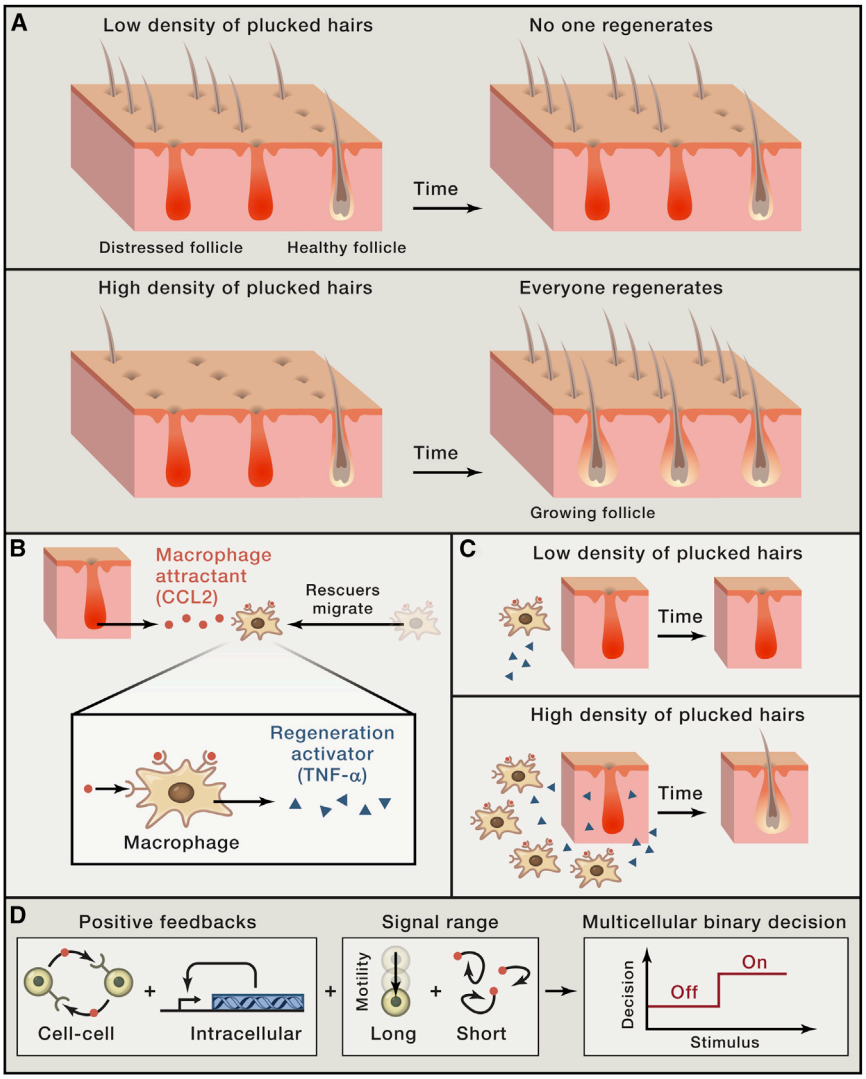

Figure 1. A Hair Follicle Can Only Regenerate in Concert with Other Follicles, but Not by Itself

(A) When the density of plucked hairs from the mouse skin is lower than a certain density (i.e., "threshold density"), no follicles regenerate. If the density of plucked hairs is higher than the threshold, all the follicles of plucked hairs ("distressed follicles") and the follicles of surrounding intact hairs ("healthy follicles") regenerate by entering growth (anagen) phase from a dormant (telogen) phase.

(B) A distressed hair follicle secretes the cytokine Ccl2. M1 macrophages sense Ccl2 and swim toward the distressed follicle.

(C) Macrophages secrete Tnf-α. Tnf-α activates regeneration of distressed and healthy follicles. Higher density of distressed follicles leads to a higher density of M1 macrophages recruited to the follicles.

(D) Main factors that a group of cells may use to collectively make a binary decision.

response (Figure 1D). In the case of the hair follicles, the short range of signaling mediated by diffusing molecules (e.g., Ccl2 and Tnf-α), the long range of signaling mediated by the motile macrophages, the spatial arrangements of the hair follicles, and the genetic circuits that control each cell's secretion and response to the different signals must all fit together to set the threshold density of hair loss and a binary multicellular response (i.e., either every follicle or no follicle regenerates) (Figure 1D). One possibility is that the macrophages make a binary decision (i.e., either move toward the distressed follicle or not) while the follicles are incapable of making any binary decisions. Another possibility is that a distressed follicle measures the density of macrophages surrounding it in such a way that it only regenerates when there is a sufficiently large density of macrophages.

Chen et al. (2015) and other recent studies (Hart et al., 2014; Sgro et al., 2015) motivate us to investigate how multiple cells, each with its own unique genetic circuit, can together achieve a collective function (e.g., a group of cells making a binary decision) that is analogous to certain behaviors of unicellular genetic circuits (e.g., a bistable genetic circuit). A key question is if there are other unicellular behaviors, which are governed by networks of genes that multicellular systems mimic with networks of communicating cells. A promising way to address this question is by building genetic circuits and cell-cell communications to reveal what sorts of multicellular behaviors can arise from them (Regot et al., 2011; Youk and Lim, 2014). An exciting outcome of this approach might be a realization that only a very small collection of genetic circuits and cell-cell interactions can yield a wide variety of collective behaviors of cells in nature.

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REFERENCES

Chen, C.-C., Wang, L., Plikus, M.V., Jiang, T.X., Murray, P.J., Ramos, R., Guerrero-Juarez, C.F., Hughes, M.W., Lee, O.K., Shi, S., et al. (2015). Cell *161*, this issue, 277–290.

De Monte, S., d'Ovidio, F., Danø, S., and Sørensen, P.G. (2007). Proc. Natl. Acad. Sci. USA *104*, 18377–18381.

Hart, Y., Reich-Zeliger, S., Antebi, Y.E., Zaretsky, I., Mayo, A.E., Alon, U., and Friedman, N. (2014). Cell *158*, 1022–1032.

Jahoda, C.A., and Christiano, A.M. (2011). Cell *146*, 678–681.

Ng, W.L., and Bassler, B.L. (2009). Annu. Rev. Genet. *43*, 197–222.

Pai, A., Srimani, J.K., Tanouchi, Y., and You, L. (2014). ACS Synth. Biol. *3*, 220–227.

Regot, S., Macia, J., Conde, N., Furukawa, K., Kjellén, J., Peeters, T., Hohmann, S., de Nadal, E., Posas, F., and Solé, R. (2011). Nature *469*, 207–211.

Rotem, E., Loinger, A., Ronin, I., Levin-Reisman, I., Gabay, C., Shoresh, N., Biham, O., and Balaban, N.Q. (2010). Proc. Natl. Acad. Sci. USA *107*, 12541–12546.

Sgro, A.E., Schwab, D.J., Noorbakhsh, J., Mestler, T., Mehta, P., and Gregor, T. (2015). Mol. Syst. Biol. *11*, 779.

Youk, H., and Lim, W.A. (2014). Science *343*, 1242782.