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Sending Mixed Messages for Cell Population Control

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Abstract

Cells often receive signals to proliferate but how population density is controlled is unclear. Hart et al. (2014) now show that a single secreted molecule that instructs both proliferation and death in T-cells establishes a bistable response: the population is driven to either extinction or to a homeostatically defined density.

Cells often behave as a collective, communicating with one another by secreting signaling molecules that act through autocrine and paracrine circuits. Although systems biology has uncovered many regulatory circuits that enable autonomous behaviors of cells, less is known about the common regulatory motifs used for communication among cells and the collective behaviors that they enable. Cell proliferation, for instance, is often regulated by extracellular signals, but how proliferation is controlled such that the cell population does not expand indefinitely (until all resources are depleted), remains an open question. In this issue of *Cell*, Hart et al. (2014) use mathematical models and experiments on T-cells to reveal how a population of cells can use an autocrine circuit to establish a bistable homeostasis that drives a population to either a state of low density or to a stably maintained state of high density that is lower than the maximum density allowed by available resources. Surprisingly, the underlying mechanism relies on a secreted extracellular signaling molecule that instructs cells to simultaneously perform two opposing tasks – cell proliferation and death. Such paradoxical signals encoded by a single extracellular molecule exist in many multicellular systems but so far their general purpose has been unclear.

To study cell population growth, the authors establish *in vitro* cultures of $CD4^+$ T-cells with a wide range of starting densities, and find that a population always expands or shrinks over time until it converges to one of two possible densities (Figure 1A). A population with a sufficiently low initial density shrinks to near extinction (LOW-state). If the initial density is above a certain threshold, however, the population density eventually converges to a single stably-maintained high value (HIGH-state). Crucially, the HIGH-state's density is lower than the maximum density allowed by available resources. Thus the population actively senses and regulates its density in a homeostatic manner instead of passively expanding.

What are the signals that could encode such information? $CD4^+$ T-cells secrete, sense, and consume the cytokine Interleukin-2 (IL-2); hence a larger population density can potentially

lead to a higher extracellular concentration. Moreover, the authors speculate that the key to homeostasis lies in a known paradoxical role of IL-2: IL-2 promotes both the proliferation and apoptosis of T-cells (Dai et al., 1999; Wang et al. 1996

Why is it advantageous for one molecule to control two opposing tasks? By applying a mathematical model for alternative ways to generate homeostasis, the authors show that using just a single secreted molecule is not necessary, but it makes the homeostasis more robust against perturbations such as sudden changes in the concentration of IL-2. Intuitively, if a cell uses a single molecule and makes a mistake in secreting, consuming, or responding to it, then this mistake will likely only affect the proliferation and death rates in a proportional fashion that still preserves the crucial balance needed for homeostasis. However, using two distinct molecules that independently control the two opposing processes means that the proportionality between the two rates can be disrupted in many ways because the two molecules are uncoordinated. An intriguing question is whether this principle - “one controller is more robust than two” - is generalizable to other systems in which maintaining a proportionality between two processes is crucial. A related question is how many different functions, either opposing or cooperating, can be optimally assigned to a single molecule and in which environmental contexts it can optimally function.

The observed IL-2 controlled homeostasis is unlikely to entirely explain *in vivo* T-cell homeostasis. Numerous cytokines besides IL-2 influence the proliferation and death of T-cells. Moreover T-cells without IL-2 can maintain homeostasis in mice (Quiel et al. 2011). Nonetheless, despite other possible mechanisms, this work demonstrates that IL-2’s paradoxical effect is sufficient to yield homeostasis. Moreover, *in vitro* cultures of immune cells enable deconstructing more complex *in vivo* circuits into smaller circuit modules whose dynamical behaviors can be studied in a controlled and systematic manner as described here. Of particular interest is investigating at a single-cell level, how autocrine and paracrine signaling between immune cells affect the population dynamics as a function of spatial organization of cells, different cytokines and receptors, and multiple cell types (Figure 1D). Moreover, systematically increasing the complexity of the *in vitro* culture by increasing the diversity of cytokines and immune cells may reveal the dynamics of *in vivo* immune systems. Such a bottom-up reconstitution of multicellular systems may also provide insights into how autocrine and paracrine signals shape population dynamics (Gregor et al. 2010). Examples include the Allee effect in ecological systems and embryonic differentiation governed by factors like BMP (Haskel-Ittah et al., 2012) and Shh. We may also gain insight into how defects in population control affect diseases such as cancer and autoimmunity (Feinerman et al., 2010).

Hart et al. highlight the importance of quantitative systems-level approaches in analyzing dynamics of multicellular systems. We typically represent transcriptional networks with “wiring diagrams” that, for many small networks, are sufficient for understanding the network’s main features without math. But for multicellular systems, quantitative features such as the spatial arrangements of cells, and variations in intercellular signals, make rigidly fixed wiring diagrams insufficient. Disentangling various intercellular signals and isolating which cell talks to which require systematically perturbing and rewiring intercellular and intracellular connections (Youk and Lim, 2014). But perhaps the most important challenge

is identifying the minimal set of parameters among the immense number of components, and then showing that this set is necessary and sufficient for producing the main features of the multicellular system. Engineering multicellular behaviors with such a set of minimal elements is a promising way to test if we truly understand principles of multicellular systems (You et al. 2004; Liu et al., 2011).

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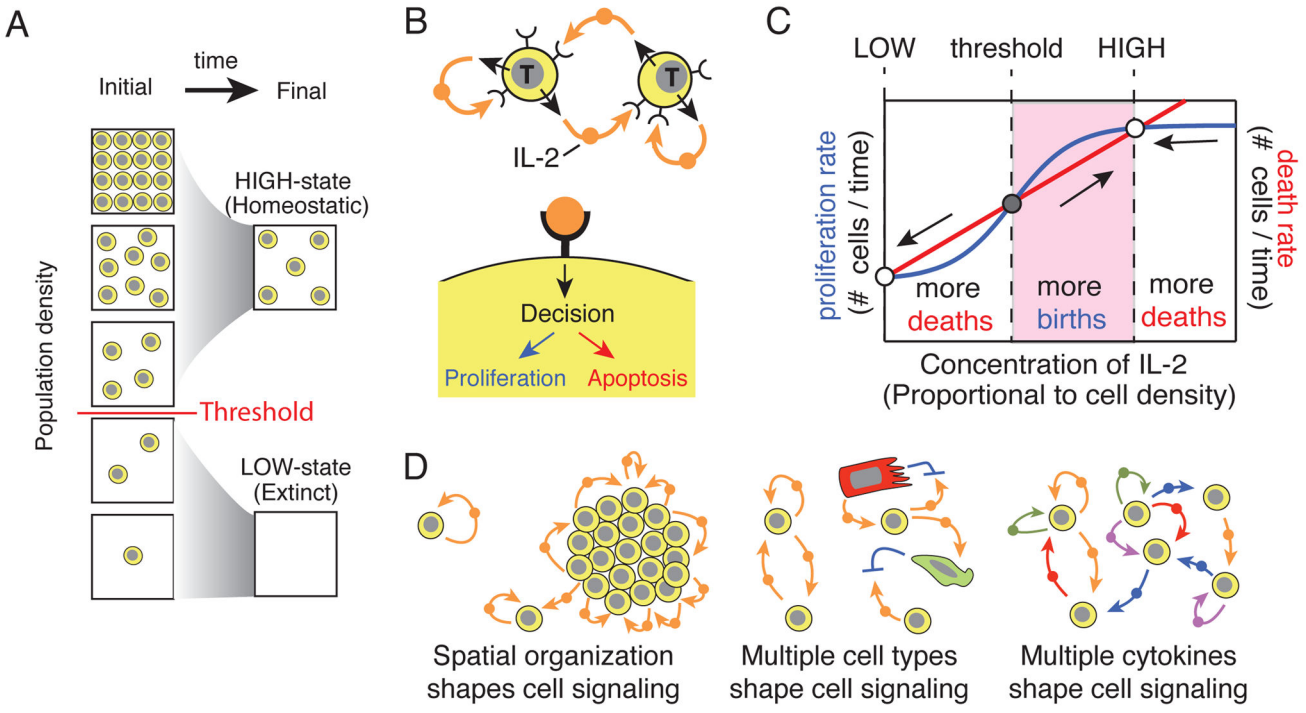

Figure 1. Autocrine and paracrine signaling via IL-2 establishes bistable homeostasis of a T-cell population

(A) A population of T-cells (yellow circles) with a starting density that is lower than the threshold goes extinct (LOW-state). A population with a starting density that is higher than the threshold converges to and is stably maintained at the HIGH-state with a homeostatically defined density.

(B) $CD4^+$ T-cells secrete, sense, and consume the cytokine IL-2 (orange circle) that promotes both their proliferation and apoptosis.

(C) When T-cells consume IL-2 at a constant rate, balancing the non-linear proliferation rate (blue) and the linear death rate (red) of T-cells enables a bistable homeostasis. This principle also underlies a more complex scenario in which T-cells' consumption rate of IL-2 increases with more IL-2. Open and closed circles represent stable and unstable fixed points respectively. Arrows show direction of population expansion or shrinkage over time.

(D) Main factors affecting autocrine and paracrine communication.