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Design principles of paradoxical signaling in the immune system

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A widespread feature of cell-cell signaling systems is paradoxical pleiotropy: the same secreted signaling molecule can induce opposite effects in the responding cells. For example, the cytokine IL-2 can promote proliferation and death of T-cells. The role of such paradoxical signaling remains unclear. We suggest that this mechanism provides homeostatic concentration of cells, independent of initial conditions. The crux of the paradoxical mechanism is the combination of a positive and a negative feedback loops creating two stable states - an OFF state and an ON state. Experimentally, we found that CD4+ cells grown in culture with a 30-fold difference in initial concentrations reached a homeostatic concentration nearly independent of initial cell levels (ON-state). Below an initial threshold, cell density decayed to extinction (OFF-state). Mathematical modeling explained the observed cell and cytokine dynamics and predicted conditions that shifted cell fate from homeostasis to the OFF-state. We suggest that paradoxical signaling provides cell circuits with specific dynamical features that are robust to environmental perturbations.