Stem cells

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Voices carry

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Analysis of cell–cell communication between embryonic stem cells using a combination of experiments and modeling shows that cells can communicate important messages over much larger distances than previously known, exhibiting quorum-sensing-like behavior.

The signals that cells send and receive via physical interactions, or at a distance via diffusible ligands, are critical for stem-cell fate determination. The indefatigable rise of high-throughput single-cell measurement technologies has offered unprecedented resolution with which to study the connections between cell fates and cell–cell communication[1,2]; however, predicting which cells are in active communication is a key challenge. In particular, we can measure internal or cell surface proteins, or (nascent) gene expression inside a cell, which may be indicative of signals received by that cell, but the identities of the signal-sending cells remain unclear and difficult to track. To address this critical question, Daneshpour et al.[3] combined mathematical modeling with experiments to show that embryonic stem (ES) cells control their fates via communication over distances larger than anyone would have imagined.

Where experimental methods to investigate cell–cell communication have lagged, computational methods to infer it from single-cell genomics data have stepped in[4]. Mathematical modeling offers an ability to predict beyond data, and has revealed ways in which cell–cell communication can tune the heterogeneity among a population of cells[5] or break the symmetry of homogenous populations of cells[6]. Typically, signaling that dictates mammalian cell fate decision-making is expected to act locally, involving coordination between small populations of cells. In contrast, microbial cell–cell communication can result in quorum sensing: macro-scale changes to phenotypes resulting from communication between large populations of cells. In the presence of multiple interacting species, complex behaviors emerge[7]. With the notable exception of hair follicle regeneration[8], quorum sensing has rarely been observed in stem-cell biology as a means of determining fates. In an attempt to infer who signals to whom, and over what distances, Daneshpour et al.[3] seeded ES cells into culture at different densities, then left the dishes undisturbed for several days. They revealed that while differentiating (but not while self-renewing), ES cells seeded above a critical population density communicated over at least millimeter-scale distances: a quorum-sensing-like phenomenon (Fig. 1).

Through an exemplary combination of theory and experiments, the authors demonstrate that ES cell quorum sensing relies on centimeter-scale population densities and the presence of a secreted 'survival factor'. Stochastic modeling of the stem-cell population dynamics in light of this survival factor predicts the density threshold below which cells will die but above which cellular division is enabled. Crucially, local communication (within or between neighboring colonies) cannot alone account for the collective growth: communication must occur over centimeter-scale distances via a survival factor that diffuses this far. Drawing on the stochastic model to complement experiments, Daneshpour et al.[3] show that the population density and the medium volume dictate a phase boundary between population growth and extinction. Finally, through a careful process of

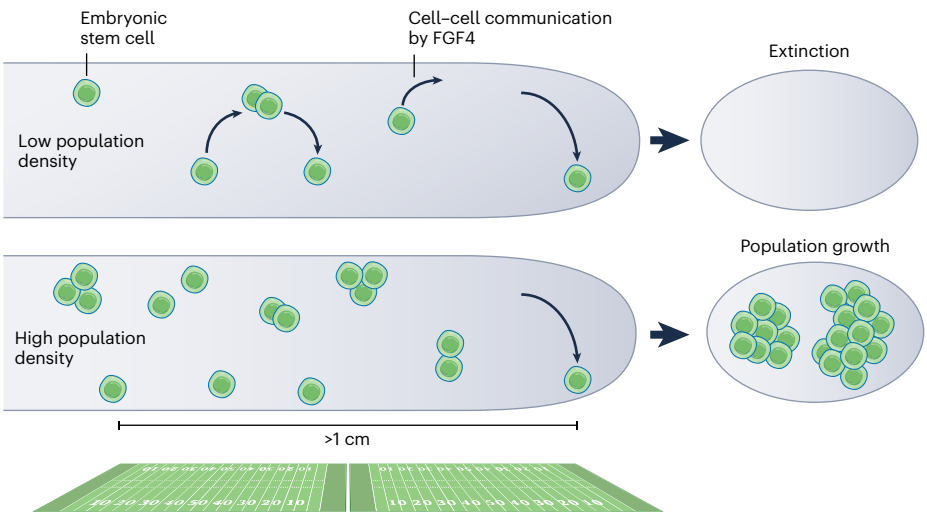

Fig. 1 | Embryonic stem-cell quorum sensing during differentiation. Embryonic stem cells communicate via FGF4 while differentiating. If the long-range (centimeter-scale) population density is a below a threshold, the entire stem-cell population will go extinct; but above the threshold, the population will survive and grow. The range of cell–cell communication observed is equivalent on a human scale—to communicating across the length of approximately two football fields.

deduction – first by narrowing down the range of possible molecular weights and diffusion lengths of this survival factor, and then by identifying candidates through RNA sequencing – the authors revealed fibroblast growth factor-4 (FGF4) as the survival factor (Fig. 1). Moreover, communication via FGF4 involves the Hippo signaling pathway by activating Yes-associated protein-1 (YAP1), which was found to be necessary for population growth.

The principal impact of the current study is undoubtedly the demonstration of centimeter-scale communication among differentiating stem cells. This immediately raises the questions of whether other ligands diffuse this far, and if so, what cell fates they might control. An advantage to studying these questions in ES cells is the ease with which we can control them in vitro; this is not always the case, for example with hematopoietic stem cells or developing organs. A move towards in vivo stem-cell communication assays will be important in future work, although challenging, with organoids potentially serving as a bridge[9].

A great strength of the current study lies in its conceptual simplicity, both experimental and theoretical. Inevitably, to achieve this, assumptions were made. The model does not consider the committed progeny of ES cells. Future work will need to take this into account, as well as the role that lineage feedback plays in regulating cell fates[10], especially if committed progenitors secrete FGF4. Cellular noise is currently modeled at the level of the population, not the single cell. Single-cell noise could take many forms (for example, via heterogeneous division rates or FGF4 sensing). Although the current results might not be affected – that is, if the central limit theorem holds – in future work it will be important in certain scenarios to consider single-cell noise, for example if a greater diversity of fates is accessible.

Recent genomics technologies have exalted the single cell, sometime at the expense of multicellular phenotypes such as cell–cell communication. Yet multicellular phenotypes underlie everything from organ development to immune responses and cancer progression. The findings by Daneshpour et al.[3] help us zoom out from this cell-centric view of biology, demonstrating the remarkable ability of stem cells to let their voices carry. We ought to hush hush and listen, for they surely have more to say.

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Competing interests

The author declares no competing interests.