Embryonic self-fracking

Mammalian embryos use controlled hydraulic fracturing to sculpt their shape

By Marino Arroyo*1,2 and Xavier Trepát1,3,4,5

From a broken bone to a major earthquake, the fracture of a material usually means trouble. However, in some practical applications engineers have learned how to harness the mechanisms of fracture. This is illustrated by the well-known process of hydraulic fracturing, or “fracking,” in which injection of pressurized fluid in shale rocks opens cracks to extract oil or gas (1). On page 465 of this issue, Dumortier et al. (2) show that the developing mouse embryo uses this same principle to transiently disrupt its shape and sculpt a more complex one. Fracking is the key mechanism that enables the early embryo to develop its first symmetry axis, a key stage in fetal morphogenesis.

During the first days of development, the preimplantation mammalian embryo is an aggregate of cells that undergo division while remaining compact and radially symmetric (see the figure). Radial symmetry is first broken when the embryo becomes a blastocyst—a structure composed of a fluid-filled lumen called the blastocoel, an enveloping cellular layer called the trophectoderm, and an inner cell mass that contains embryonic progenitors (3). As development proceeds, the trophectoderm gives rise to the placenta, and the inner cell mass progenitors give rise to the fetus. Over the past decade, an increasingly detailed description of the molecular changes that accompany symmetry breaking during the formation of the blastocyst have been provided (4). However, symmetry breaking is ultimately a mechanical event, and understanding this requires a mechanical framework.

To provide such a framework, Dumortier et al. performed high-resolution live imaging of the formation of the blastocyst. After the fifth round of cell division, they observed the synchronous appearance of hundreds of bubbles at cell-cell junctions. These bubbles were filled with pressurized water, and their formation was impaired by disruption of cell polarity, reversal of the osmotic gradient, and inhibition of ion transport through sodium/potassium pumps. During bubble formation, the spatial distribution of the main cell-cell adhesion protein of the blastocyst, E-cadherin, is reorganized to accumulate at the edges of the bubbles. Thus, these bubbles form through hydraulic fracturing: Pressurized fluid is injected between two previously cohesive cell membranes, causing their separation and the displacement of cell-cell adhesion proteins. Similar pressurized fluid bubbles that disrupt cell-cell and cell–extracellular matrix interfaces have been observed in vitro as a result of fluid pressure in the extracellular matrix (5), osmotic perturbations (6), or directed ionic transport (7).

How does the embryo transition from hundreds of small fluid-filled microlumens at all cell-cell junctions to a single large lumen, the blastocoel? Dumortier et al. found that after a homogeneous growth phase, some microlumens started growing at the expense of others, until a single lumen took over the rest to become the blastocoel. Microlumens thus coarsened over time, as vinegar and oil droplets do in a salad dressing, in a process reminiscent of Ostwald ripening (8). Classical ripening proceeds by diffusive mass transport from the smaller droplets, which experience higher pressure following Laplace’s law (relating size, pressure, and surface tension), toward larger ones. The observations of Dumortier et al. support an analogous physical picture, with the exception that in the mouse embryo, surface tension is produced by the contractile cell surface, and mass transport between lumens proceeds by means of fluid flow through a hydraulically connected network of intercellular gaps rather than from diffusion.

These processes and nonspecific mechanisms of hydraulic fracturing and coarsening do not explain the precise positioning of the blastocoel. To address this, the authors combined experimental and theoretical approaches. By patterning stickiness and contractility, they were able to direct microlumens coarsening toward less adhesive and less contractile cell-cell junctions. They found evidence suggesting that blastocoel positioning was guided by contractility. Dumortier et al. thus propose that the blastocoel is robustly positioned by hydraulically opening potential lumens throughout the embryo and then delicately guiding the coarsening process through differences in cell contractility, in an intriguing interplay between physical and biological patterning.

It is compelling to ask whether profuse fracturing followed by coarsening is a general mechanism of lumogenesis in biol-

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Fracking in the mouse embryo

To establish its first symmetry axis, the mouse embryo self-fractures by pressurizing (p) fluid between cell-cell junctions. Coarsening of the resulting microlumens is then precisely directed by spatially modulating cytoskeletal contractility and thus cellular surface tension.
11. A. Lucantonio, G. Noselli, X. Trepat, A. DeSimone, M. Arroyo, Z. Xue, M. Arroyo, C. E. Morris, J. A. Wang, V. S. Markin, E. Latorre, and L. Casares demonstrated remarkable control of blastocoel positioning through tuning hydraulic resistance or ionic transport. Owing to its incompressibility and the diverse mechanisms available to transport it, water is emerging as a powerful tool for embryos to sculpt their shape. Besides direct mechanical action, fluid pressure can trigger mechanotransduction signaling, providing an additional layer of control between embryonic growth and hydraulic principles (10). At first glance, morphogenesis and fracture seem incompatible concepts; one is about construction, and the other is about destruction. The study of Dumortier et al. reconciles these two concepts by showing that embryos have evolved mechanisms with which to exquisitely self-fracture and self-heal, with the ultimate goal of creating new functional shapes. The physical principles used by embryos to control hydraulic fracture are general and thus could inspire the design of new materials or improve engineering processes (11).

REFERENCES AND NOTES

1. M. B. Smith, C. Montgomery, Hydraulic Fracturing (CRC Press, 2015).
2. J. G. Dumortier et al., Science 365, 465 (2019).
3. Q. Chen, J. Shi, Y. Tao, M. Zernicka-Goetz, Nat. Commun. 9, 1819 (2018).
4. Z. Xue et al., Nature 500, 593 (2013).
5. L. Casares et al., Nat. Mater. 14, 343 (2015).
6. C. E. Morris, J. A. Wang, V. S. Markin, Biophys. J. 85, 223 (2003).
7. E. Latorre et al., Nature 563, 203 (2018).
8. W. Ostwald, Z. Phys. Chem. 34, 495 (1900).
9. S. Sigurbjörnsdóttir, R. Mathew, M. Leptin, Nat. Rev. Mol. Cell Biol. 15, 665 (2014).
10. C. J. Chan et al., Nature 571, 112 (2019).
11. A. Lucantonio, G. Noselli, X. Trepat, A. DeSimone, M. Arroyo, Phys. Rev. Lett. 115, 188105 (2015).

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Herring were processed for oil in Norway in 1911. Industrial fishing is one example of a new selection pressure caused by humans that may induce rapid evolutionary change (8).

ECOLOGY

Fishing for answers

Naturally existing genetic variation promotes rapid evolution under strong anthropogenic selection

By Christian Jørgensen and Katja Enberg

One hallmark of the Anthropocene is a rapid change in the ways our bipedal species affects the wild cohabitants on Earth. Emerging evidence on many fronts suggests that human-induced environmental change can lead to marked evolution on decadal or even shorter time scales. One eye-opening study from 2002 simulated intensive fishing and reported a twofold difference in body weight after just four generations of selectively harvesting either small or large individuals (1). Merely documenting that rapid evolution takes place, however, falls short of deciphering how it occurs at a mechanistic level—a prerequisite for predicting evolution in other cases. On page 487 of this issue, Therkildsen et al. (2) show that genomic changes manifested during the original 2002 experiment partly aligned with variation along a natural gradient in the wild, but that strong selection also quickly eroded genetic variance.

Behind the many documented facets of contemporary global change—species invasions, land-use modifications, climate change—lie untold stories of new and strong selection pressures (3). “New selection pressure” is a gentler way of saying that individuals die sooner or reproduce less. Other individuals that better tackle the new environment pass on their heritable traits; thus, the population evolves and perhaps persists. This is how the ancestors of existing species have outrun every environmental challenge until now. The current rate of human-driven ecological changes, however, raises a key question: Is evolution fast enough to keep up, or will these strong selection pressures curtail biodiversity?

A first approach to understanding evolutionary change is phenotype-centric and starts from knowledge of how organisms function in their environment (for example, physiology, behavior, and ecology). The challenge here is to decipher how phenotypes with certain heritable traits survive or reproduce better than alternative phenotypes. Therkildsen et al. studied the Atlantic silversides, a fish species that exists along a latitudinal diversity gradient wherein clever experiments have demonstrated advantages of fast growth in northern populations driven by a short productive season (4). By contrast, south-