Converging development: How cell paths unite in the embryo

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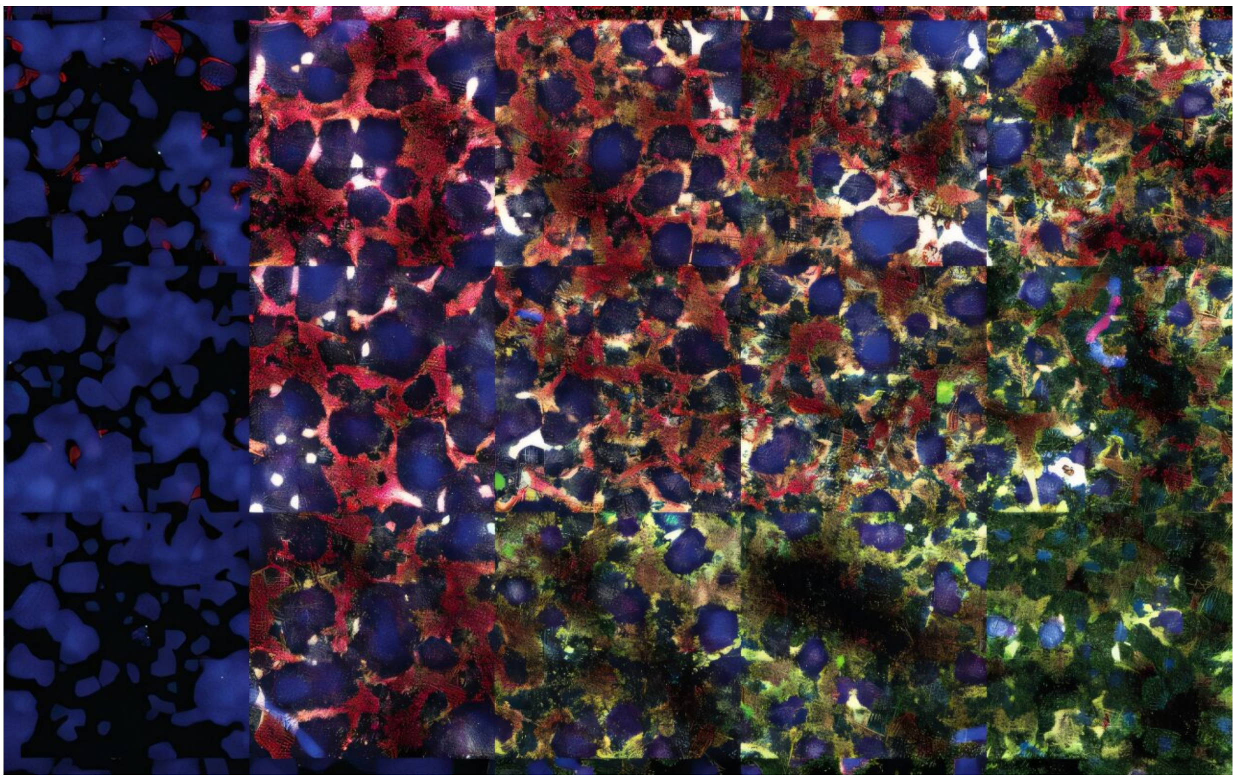


Human embryonic stem cells responding to different combinations of cues and forming different fates. Credit: Ollie Inge

By tracking the fate of individual embryonic stem cells, researchers have found that endoderm cells—early embryonic cells that give rise to tissues such as the gut and lungs—originate from multiple converging developmental paths challenging long-held assumptions about cells following linear trajectories.

When planning a trip, it's rare that you don't have a choice of route. One may be more direct, another more scenic; but regardless of the time or route taken, the destination is the same. This concept of converging paths can also be observed in developmental biology, in the routes embryonic cells take to become specialized.

As Crick group Leader Silvia Santos describes, "In early development, during a phase called gastrulation, the embryo transforms from a single layer of cells into a multi-layered structure. Three layers of cells form, known as the germ layers, that go on to become the different tissues of the body, from the vasculature to the nervous system.

"But how these germ layers form has been the subject of disagreement among scientists. In particular, scientists have not conclusively determined how cells specialize to become part of the endoderm, which is the innermost layer and goes on to form many important internal organs including the gut, the liver and the lungs."

Routes on the map

Several models of cell fate lineages have been presented, with some researchers proposing a "traditional" straight path where stem cells are guided and gradually restricted by signaling cues. Others have suggested a more dynamic model, where cell fate remains more flexible and subject to real time positioning and cues, meaning a cell might arrive at an endoderm fate via another developmental route.

In new research published today in *Developmental Cell*, Santos's team combined a range of experimental techniques—single cell transcriptomics, quantitative live cell imaging and mathematical modeling—to track cell fate and determine which of these paths is the right one.

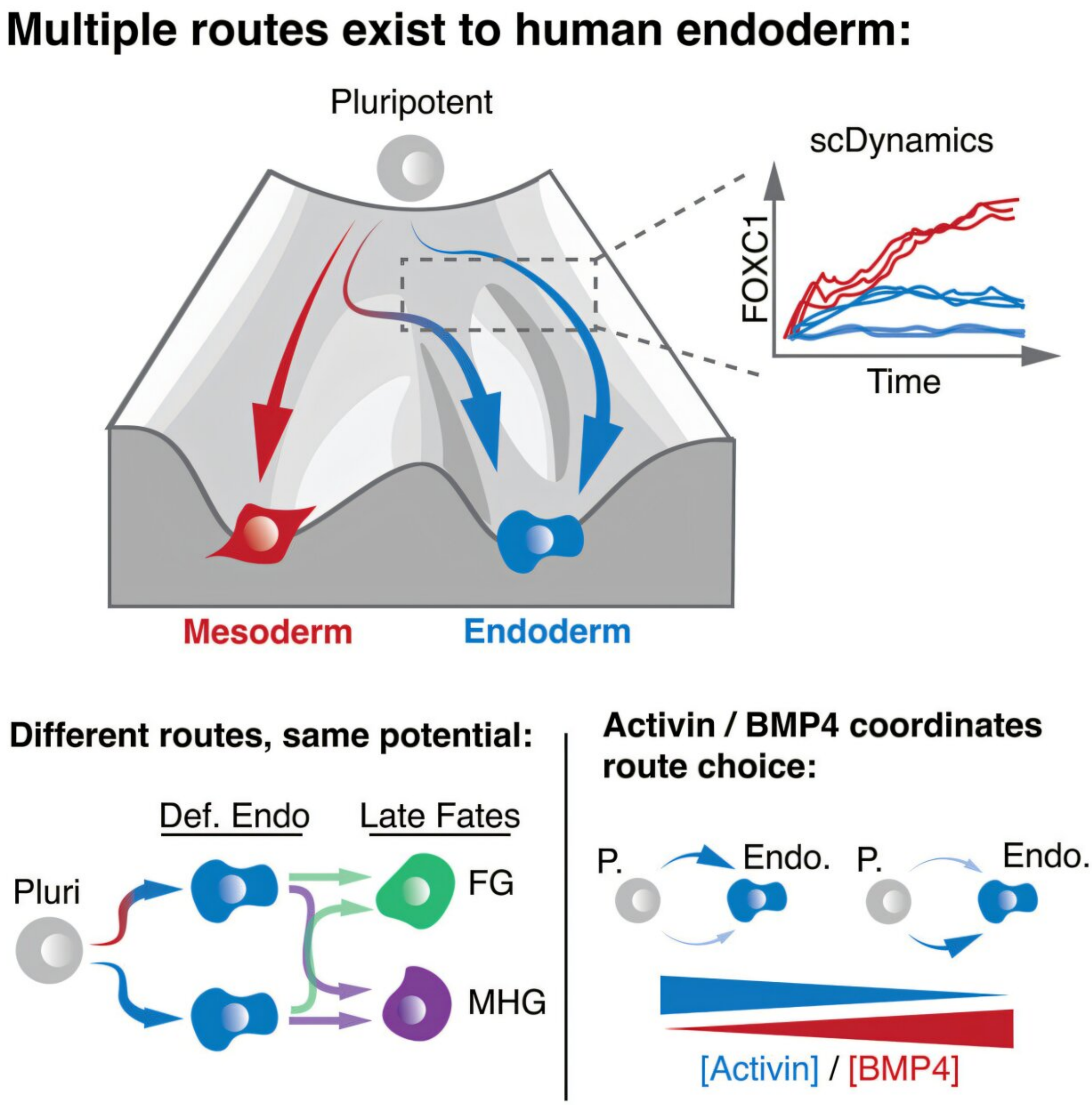
They found that there was no singular path, and these theories were not competing explanations but complementary snapshots of human development. They've provided a unifying model for a longstanding debate that reconciles conflicting models of mesoderm and endoderm specification—in some way, everyone was right.

Merge ahead

The team also observed the influence of two important signaling molecules, Activin and BMP4, that worked both together and in competition to determine which route the cells would take.

"We observed certain time windows when cells were responsive to these signals," explains Ollie Inge, who led the study. "Their relative concentrations during this period determined which route the cells would take, much like a sat nav determining which way to go based on current traffic advice."

Inge identified BMP4 as the major driver of cell lineage, as its relative concentration to Activin was pivotal in steering cells towards direct endoderm specialization or via a mesoderm state.



Credit: *Developmental Cell* (2025). DOI: 10.1016/j.devcel.2025.08.009

The mystery remains as to why cells can take different routes towards the same fate, especially when some paths seem more straightforward.

"We think this is a sign of how important a developmental stage is," suggests Santos. "Failure to differentiate into the germ layers during gastrulation is a major contributor to pregnancy loss and without correct formation of the endoderm layer, embryos wouldn't then be able to form vital internal organs. So, convergence of these cell lineages provides a robust foundation for our development."

"In fact, so important are these early cell populations that being able to efficiently derive them in the lab is considered the holy grail of regenerative medicine, and this brings us a step closer."

"While we've addressed some important questions about our early development, we've also further highlighted the complexity of cell fate decisions," adds Inge.

"It was only by taking an interdisciplinary approach—bringing together (transcript)omics, mathematical and imaging techniques that we could understand, at the level of an individual cell, how embryonic cells choose their fates and uncover key blueprints for early development."

More information: Oliver C.K. Inge et al, Combinatorial BMP4 and Activin direct the choice between alternate routes to endoderm in a stem cell model of human gastrulation, *Developmental Cell* (2025). DOI: 10.1016/j.devcel.2025.08.009. www.cell.com/developmental-cel … 1534-5807(25)00529-5

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