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> …a population of visceral endoderm cells contributes to the developing embryo.

7.5-day-old mouse embryo in which all visceral endoderm cells express green fluorescent protein (GFP; green), revealing a scattered population of cells that contributes to the embryo. Single midline optical section from a Z-stack of images (left). Three-dimensional reconstruction of a Z-stack of images (right). Image courtesy of A.-K. Hadjantonakis, Sloan-Kettering Institute, New York, USA.

DEVELOPMENT

Dogma overturned

According to every textbook of embryology, an early mouse embryo is composed of two cell layers: the epiblast (ectoderm) and the visceral endoderm, which covers the epiblast. During gastrulation, the epiblast generates two other cell layers (endoderm and mesoderm) and, ultimately, gives rise to the entire embryo. By contrast, the visceral endoderm contributes only to extraembryonic structures, such as the yolk sac. But Kat Hadjantonakis and colleagues have now overturned this dogma by discovering that a population of visceral endoderm cells contributes to the developing embryo.

Previous studies have suggested that embryonic endoderm cells reach the outer surface of the embryo and move as a continuous sheet to displace visceral endoderm cells to the periphery of the embryo. To study these movements in detail, the authors genetically labelled visceral endoderm cells by expressing green fluorescent protein (GFP) under the control of *α-fetoprotein* (a marker of visceral endoderm) and carried out time-lapse video microscopy in live embryos.

The three-dimensional reconstructions of the imaging data revealed that the GFP-positive visceral endoderm cells at the posterior and distal part of the embryo are not displaced to extraembryonic regions but remain associated with the epiblast. Single GFP-negative epiblast-derived endoderm cells intercalate between the GFP-positive cells, which results in a scattered pattern of GFP-positive cells at this location. These results, which were confirmed by two additional genetic labelling approaches, show that the scattered population of cells that overlays the epiblast is not of epiblast origin but derives from the visceral endoderm.

Tight junctions and adherens junctions at the interface between neighbouring GFP-positive cells that are undergoing separation, which were visualized using specific markers, are remodelled to facilitate the cell dispersal process. Furthermore, the scattered visceral endoderm cell population continues to proliferate, although at lower rates compared with epiblast-derived cells. But what happens to this cell population later in development?

Imaging of embryos at later stages, at around embryonic day 8.75 (E8.75), showed that the visceral endoderm-derived cells incorporate into the columnar epithelium of the gut tube, which has always been thought to derive exclusively from epiblast cells. As the authors point out in reference to these visceral endoderm-derived cells, "it will be important to determine their exact location and whether they are molecularly and functionally distinct from epiblast-derived definitive endoderm cells during homeostasis and disease states". For now, however, we can start to update the textbooks.

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ORIGINAL RESEARCH PAPER Kwon, G. S., Viotti, M. & Hadjantonakis A.-K. The endoderm of the mouse embryo arises by dynamic widespread intercalation of embryonic and extraembryonic lineages. *Dev. Cell* **15**, 509–520 (2008)