

# “Induction and Patterning of the Primitive Streak, an Organizing Center of Gastrulation in the Amniote,” by Takashi Mikawa, Alisa M. Poh, Kristine A. Kelly, Yasuo Ishii and David E. Reese

“Induction and Patterning of the Primitive Streak, an Organizing Center of Gastrulation in the Amniote,” (hereafter referred to as “Induction”) examines the mechanisms underlying early amniote gastrulation and the formation of the primitive streak and midline axis. The review, authored by Takashi Mikawa and colleagues at Cornell University Medical College, was published in *Developmental Dynamics* in 2004. The article primarily discusses chick embryos as a model organism for nonrodent amniote gastrulation, although it intermittently touches on nonamniote gastrulation for comparative purposes. “Induction” attempts to explain the initiation of cell differentiation and embryo organization, one of the most intriguing processes of embryology.

The primitive streak is an elongated group of mesodermal cells that move inward toward the center of the early embryo, delineating the organism’s anterior and posterior ends. The authors mainly explore the existing knowledge concerning the initiation of early primitive streak formation and the mechanisms regulating its extension and directional diversification. By gaining a better understanding of the function of the primitive streak and the main axes of development, they hope to contribute to the bigger picture of amniote embryology—that is, the early development of reptiles, birds, and mammals inside the amniotic fluid. The graphics included in the paper feature explanatory diagrams and images from the Hamburger-Hamilton Stages of chick embryogenesis.

The introduction provides a brief, general background to the early stages of embryonic development. The authors explain that the chick zygote undergoes division that produces a small disc of cells called the blastodisc, which eventually results in the formation of three germ layers: the ectoderm (outer), mesoderm (middle) and endoderm (inner). The primitive streak, which is made up of bottle-shaped mesenchymal cells, forms at the posterior of this disc and serves as the basis for gastrulation in amniotes. The formation of the streak determines the direction of the anterior-posterior (AP) axis and the more specific location of the midline axis where the notochord of the chick will eventually lie.

While the authors admit that, as of yet, little is known about the mechanisms that initiate the formation of the primitive streak, there are a number of hypotheses pertaining to the directly-related formation of the axes in the embryo. These axes are the AP, the midline, and the dorsal-ventral (DV) axes. The authors suggest that gravity and electricity may play a role together, or separately, in delineating the location of the AP and DV axes. Membrane potential and pH gradients are also thought to influence the formation of the axes. Citing a 1960 experiment by Nelson T. Spratt, Jr. and Helmut Haas, the authors remark that subdivisions of the blastodisc each give rise to a separate chick embryo, suggesting plasticity of the axes during the early stages of development.

The discussion of axis formation leads into an examination of the induction of the initial primitive streak, an event that is thought to drive the demarcation of the midline axis. Studies in whole chick embryo cultures have implicated the posterior marginal zone (PMZ) of the embryonic disc as a likely site of primitive streak induction. The authors name a number of paracrine signaling factors and transcriptional factors which have been detected in the process and are thought to have a significant effect. However, they concede that there is still some confusion as to which cells respond to the signals and how they carry the response out. The paper discusses an early hypothesis proposed in

1990 by Claudio Stern and David Canning, who postulated that there are two distinct populations of cells that make up the early chick embryo, only one of which is capable of responding to induction signals. They suggested that these responsive cells are scattered randomly and aggregate into the initial primitive streak upon signaling from the PMZ. An alternative model, formulated after studies in 2001, describes PMZ-derived signals acting on immediately-neighboring cells, as opposed to scattered cells, to induce primitive streak formation. However, this model is still under scrutiny in order to determine how those signals specify the primitive streak within the epiblast.

After presenting these hypotheses about the formation of initial primitive streak, the authors of "Induction" discuss the streak's morphogenesis in detail. Much of this information is presented through comparison to processes in amphibians. Two studies using different fate mapping techniques are outlined in order to examine the current understanding of the morphogenetic process. The first study was carried out by Hefzibah Eyal-Giladi's lab in 1992. Eyal-Giladi used fluorescent-labeled grafting methods to trace the migration of precursor cells, and found that they first migrate toward the midline and then move anteriorly toward the middle of the embryonic disc.

The second study reviewed was performed by Yan Wei and Takashi Mikawa in 2000. This later study used *in vivo* retroviral-mediated tagging and produced labeled daughter cells. These cells were arranged perpendicular to the axis of streak extension, whereas the rest of the dividing cells were not oriented in any particular direction. To explain the phenomenon of streak extension and shaping, Wei and Mikawa proposed an interaction between three morphological processes: active cell proliferation, intercalation, and oriented cell division. A combination of these processes would produce a large number of cells, stretch cells mediolaterally, and push the elongating cell mass toward the center of the embryonic disc, as seen in the stage II primitive streak of the Hamburger-Hamilton Stages.

In the final section of the paper, the authors review the patterning of the initial primitive streak along the AP, DV, and mediolateral axes. Expression profiles of the different genes acting on the primitive streak during its formation indicate that many of them operate on very specific zones. The specified behavior of many of these genes has produced evidence both for and against the idea that gene expression at this stage is predictive of cell fate. The fact that certain genes are only expressed in very particular regions implies that their expression must also lead to the emergence of different types of cells. However, the opposing argument contends that since gene expression is dynamic and sometimes even cyclical or oscillating, it cannot be considered a definitive indicator of cell fate at this stage of ontogeny.

Another important, though largely unexplained, phenomenon noted in "Induction," is the pattern of cell death along the primitive streak midline. The authors are careful to explain that this cell death is not typical of apoptosis or necrosis; the dead cells are not digested but are instead incorporated in the streak midline during gastrulation and do not ingress. They also state that the mechanism behind this unusual pattern of cell death is unknown as of yet. However, since certain gastrulation markers are expressed in the emerging primitive streak prior to midline cell death, it seems that the future midline is in fact already established in the primitive streak at this point. Disruption of this cell death has been found to cause issues with laterality during development, so it is thought that this region of dead cells serves to separate the left and right sides of the embryonic disc.

The authors conclude "Induction" with questions for further study and highlight the importance of learning more about early primitive streak formation. They suggest that continued exploration of the topic will in turn reveal more information about the formation of the three germ layers essential for functional differentiation, and help establish a better understanding of the regulation of axis formation in embryos.

## Sources

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