

Molecular Mechanisms of Migration through the Primitive Streak

Formation of the primitive streak

The migration of chick epiblast cells to form the primitive streak was first analyzed by Ludwig Gräper, who in 1926 made time-lapse movies of labeled cells under the microscope. He wrote that these movements reminded him of the Polonaise, a courtly dance in which men and women move in parallel rows along the sides of the room, and the man and woman at the “posterior end” leave their respective lines to dance forward through the center. The mechanism for the cellular “dance” was revealed by Voiculescu and colleagues (2007), who used a modern version of cinemicrography (specifically, multiphoton time-lapse microscopy) that identified individual moving cells. They found that cells came down the sides of the epiblast to undergo a medially directed intercalation of cells in the posterior margin where the primitive streak was forming (Figure 1). And although the movement may look like a dance from far away, “at high power, it looks like a rush hour” (Stern 2007).

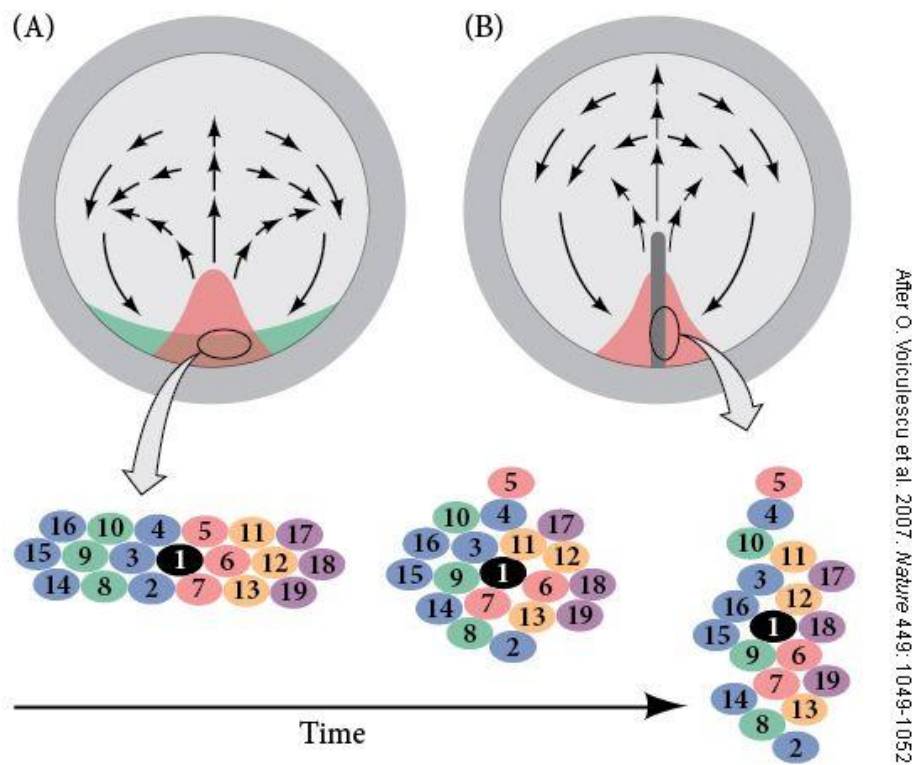


Figure 1 Mediolateral intercalation in the formation of the primitive streak. Chick embryos at (A) stage 13 (immediately prior

to primitive streak formation) and (B) stage 2 (shortly after primitive streak formation). Arrows show cell displacement toward the streak and in front of it. The pink area represents the streak-forming region; in (A), the original location of this region is shown in green. The circled areas are represented in the lower row. Each colored disc represents an individual cell, and the cells become mediolaterally intercalated as the primitive streak forms.

New studies (Lee et al 2022a) have shown that the extra-embryonic area opaca is critical in determining where this occurs. Indeed, transplanting a region of the area opaca onto the area pellucida induces the formation of a new posterior marginal zone from the area pellucida. This will create a new primitive streak. It is possible that the posterior (streak-forming) ability is a ‘default’ condition of the entire marginal zone, and that the other signals in the normal embryo act to restrict this character to the posterior position. The *VG1* gene (producing a Nodal-like protein) is important in forming the early primitive streak, and its expression is probably regulated by both BMP (negatively) and Wnts (positively). The role of gravity and biomechanical factors in this specification has yet to be studied. Once expressed, the *VG1* protein interacts with the FGF and planar WNT pathways to induce the ingression of the mesendoderm cells and their convergent extension (Lee et al 2022b).

This rush to the center is mediated by the activation of the Wnt planar cell polarity pathway in the epiblast next to Koller’s sickle, at the posterior edge of the embryo. If this pathway is blocked, the mesoderm and endoderm form peripherally instead of centrally. The Wnt pathway in turn appears to be activated by fibroblast growth factors (FGFs) produced by the hypoblast. If the hypoblast is rotated, the orientation of the primitive streak follows it. Moreover, if FGF signaling is activated in the margin of the epiblast, Wnt signaling will occur there and the orientation of the primitive streak will change, as if the hypoblast had been placed there. The cell migrations that form the primitive streak thus appear to be regulated by FGFs coming from the hypoblast, which contribute to activate the Wnt planar cell polarity pathway in the epiblast.

Migration through the primitive streak

Cells migrate to the primitive streak, and as they enter the embryo, the cells separate into two layers. The deep layer joins the hypoblast along its midline, displacing the hypoblast cells to the sides. These deep-moving cells give rise to the endodermal organs of the embryo, as well as to most of the extraembryonic membranes (the hypoblast and peripheral cells of the area opaca form the rest). The second migrating layer spreads to form a loose layer of cells between the endoderm and the epiblast. This middle layer of cells generates the mesodermal portions of the embryo and the mesoderm lining the extraembryonic membranes.

The migration of mesodermal cells through the anterior primitive streak and their condensation to form the chordamesoderm also appear to be controlled by FGF and Wnt signaling. *Fgf8* is expressed in the primitive streak and repels migrating cells away from the streak. Yang and colleagues (2002) were able to follow the trajectories of cells as they migrated through the primitive streak (see Figure 13.6) and were able to deflect these normal trajectories by using beads that released *Fgf8*.

Once cells migrate away from the streak, further movement of the mesodermal precursors appears to be regulated by Wnt proteins. In the more posterior regions, *Wnt5a* is unopposed and directs the cells to migrate broadly and become lateral plate mesoderm. In the more anterior regions of the streak, however, *Wnt5a* is opposed by *Wnt3a*, which inhibits migration and causes the cells to form paraxial mesoderm. Indeed, the addition of *Wnt3a*-secreting pellets to the posterior primitive streak suppresses lateral migration and prevents the formation of lateral plate mesoderm (Sweetman et al.

2008). By 22 hours of incubation, most of the presumptive endodermal cells are in the interior of the embryo, although presumptive mesodermal cells continue to migrate inward for a longer time.

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