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Formation of the chick primitive streak as studied in computer simulations

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Abstract

We have used a computer simulation system to examine formation of the chick primitive streak and to test the proposal (Wei and Mikawa Development 127 (2000) 87) that oriented cell division could account for primitive streak elongation. We find that this proposal is inadequate to explain elongation of the streak. In contrast, a correctly patterned model streak can be generated if two putative mechanisms are operative. First, a subpopulation of precursor cells that is known to contribute to the streak is assigned a specific, but simple, movement pattern. Second, additional cells within the epiblast are allowed to incorporate into the streak based on near-neighbor relations. In this model, the streak is cast as a steady-state system with continuous recruitment of neighboring epiblast cells, egress of cells into deeper layers and an internal pattern of cell movement. The model accurately portrays elongation and maintenance of a robust streak, changes in the composition of the streak and defects in the streak after experimental manipulation.

Keywords: Morphologenesis; Chick primitive streak; Computer simulations

1. Introduction

Formation of the primitive streak is the most important event of gastrulation in amniote (reptile, avian and mammalian) embryos. The primitive streak arises from the posterior pole of the epiblast and elongates rapidly in an anterior direction until it reaches to just beyond the center of the embryo (Fig. 1). This occurs between embryonic stage XIV and stage 3+ (Hamburger and Hamilton, 1951; Eyal-Giladi and Kochav, 1976), a period of about 9 h (Spratt, 1946). Indeed, most of this rapid elongation can be seen by cine analysis to occur over as brief a time as 3–6 h (Foley et al., 2000). Although the streak eventually regresses, it forms the essential conduit for gastrulation and serves to define the anteroposterior axis of the embryo.

Formation of the streak may involve: (i) a visible change, conformational or compositional, in *in situ* cells, (ii) new cells taking up residence in the region of the evolving streak, or (iii) a combination of these mechanisms. The speed with which the streak evolves suggests the first possibility, but careful marking experiments (Eyal-Giladi et al., 1992; Bachvarova et al., 1998; Wei and Mikawa, 2000; Lawson and Schoenwolf, 2001b) have demonstrated that cells throughout the evolving streak are derived from *Koller's sickle* (an arc of cells at the posterior edge of the epiblast—see Appendix A) and the neighboring epiblast (here termed, *sickle-associated epiblast*). Cells that contribute to the primitive streak are located at the extreme posterior margin of the epiblast prior to streak formation and then are rapidly dispersed along the posterior midline.

The mechanisms that distribute these cells and result in formation of the streak are largely unknown. It has been suggested that elongation of the primitive streak is

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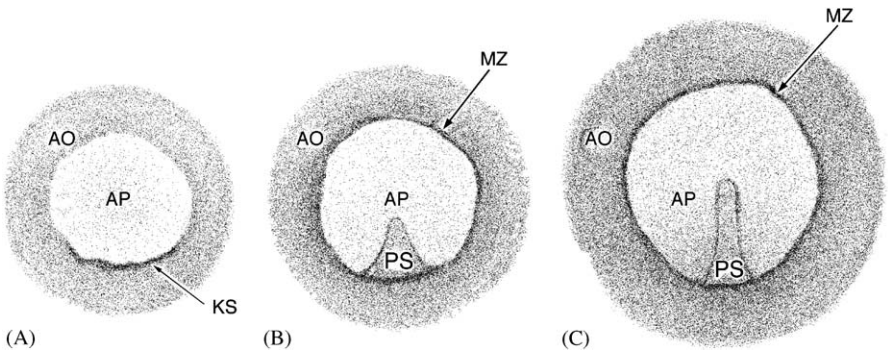

Fig. 1. Shown are representations of the dorsal surface of the chick embryo at (A) stage XIII, (B) stage 2, and (C) stage 3+. AO—area opaca, AP—area pellucida, MZ—marginal zone, KS—Koller's sickle, PS—primitive streak (after Patten, 1971).

driven by oriented cell division within this cell population (Wei and Mikawa, 2000). Here, we use a computer simulation model to distinguish this possibility from an alternative—directed migration and near-neighbor recruitment.

2. Simulations

All simulations were performed using the *Nudge*++ modeling system. Details of the modeling system and its application to the primitive streak are provided in Appendix B. In brief, cells are modeled as inelastic spheres confined to a disc. They carry out individual cellular programs and the model tissue evolves as the pooled behavior of these individual cells. Simulations are generated by specifying the individual cellular programs and observing the generated tissue patterns. Simulations are summarized in Table 1 and described in detail below.

Our interest here is elongation of the primitive streak as occurs between stage XIV and stage 3+ (Fig. 1), although some simulations have been run to later stages as needed. Preceding and contemporaneous with streak formation, the entire epiblast is engaged in a large-scale pattern of cell movements (Figs. 2 and 3; see Appendix A). Here, we distinguish this pattern of global movements from the specific actions that result in primitive streak formation, the latter being much more focused in both time and space and, we infer, differently arranged in the embryo. However, since primitive streak choreography is performed on this moving stage, we begin our simulations with these global movements and maintain them as background through all subsequent simulations.

Our simulations include a stochastic component and each simulation has been run at least ten times. Examples shown were then chosen to reflect the range of possible outcomes:

2.1. Background movements

To recreate the experimentally defined global movement pattern (see Appendix A; Gräper, 1929; Wetzel, 1929; Spratt, 1946; Eyal-Giladi et al., 1992; Hatada and Stern, 1994; Levy and Khaner, 1998; Foley et al., 2000; Lawson and Schoenwolf, 2001b; rev. Romanoff, 1960) cells throughout the epiblast were instructed to move in a position-dependent fashion that was designed to match the experimental data.

These movements produce a general elongation and relative narrowing of the posterior epiblast as seen in the embryo (Fig. 4). In general, cells are driven toward the posterior epiblast where they amass and force the characteristic elongation. The degree of elongation is an increasing function of the rate of cell movement relative to the mitotic rate (not shown).

This global pattern is maintained as a constant background program for all further simulations.

2.2. Focus on the streak

For simulations of the streak itself, we have highlighted a small cohort of cells in the posterior epiblast (designed to represent the streak precursors of Koller's sickle and the sickle-associated epiblast) of the initial (stage XIII) tissue (Fig. 5a). We have followed these precursors and their progeny as the model tissue progresses to the 12 h time point (about Stage 3+). Note that the background cell movement pattern (without any streak-specific component) causes these cells to become distributed along the posterior midline in a pattern reminiscent of the streak (Fig. 5b).[1]

[1]The global movement pattern includes a circumferential component laterally and an "updraft" from posterior to anterior in the posterior midline (see Appendix A). Clearly, this updraft will tend to distribute posterior cells to more anterior positions and thus foreshadow streak formation. However, these global movements, including the updraft, begin many hours in advance of streak formation. The updraft appears to be incidental to streak formation, although it may serve to position