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Traveling wave formation in vertebrate segmentation

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ABSTRACT

In vertebrate somitogenesis, "segmentation clock" genes (such as *her* in zebrafish, *hairy* in chick, and *hes* in mouse) show oscillation, synchronized over nearby cells through cell–cell interaction. The locations of high gene expression appear with regular intervals and move like a wave from posterior to anterior with the speed slowing down toward the anterior end. We analyze traveling wave pattern of *her* gene expression when there is an anterior–posterior gradient of one of the reaction rates in the gene-protein kinetics. We adopt a model which includes the kinetics of mRNA and proteins of *her* gene in each cell and cell–cell interaction by Delta–Notch system explicitly. We show that the observed spatio-temporal pattern can be explained if mRNA degradation, protein translation, protein transportation to nucleus occurs faster, or mRNA transcription, Delta protein synthesis occurs slower in posterior than in anterior regions. All of these gradients are those that produce longer periodicity of oscillation of clock gene expression in the anterior than in the posterior. Based on this result, we derive a mathematical formula for how the peak of gene expression moves along the pre-somitic mesoderm.

1. Introduction

Segmentation in vertebrate development proceeds through a one-by-one addition of a new somite. The time interval between the formation of one unit and the next is species-specific: 90 min for chick, 120 min for mouse, and 30 min for zebrafish. This interval is considered to be controlled by the oscillating expression of "segmentation clock genes" observed in the pre-somitic mesoderm because its period of oscillation is very close to the interval (Bessho et al., 2001; Holley et al., 2000; Jouve et al., 2000; Oates and Ho, 2002; Palmeirim et al., 1997). The molecular mechanism of their oscillatory expression is the negative feedback regulation by their own products (Giudicelli et al., 2007; Hirata et al., 2002; Holley et al., 2002; Horikawa et al., 2006). The oscillations observed within cells around the posterior end of the pre-somitic mesoderm are synchronized through the intercellular interaction between neighboring cells (Maroto et al., 2005; Masamizu et al., 2006). In the case of zebrafish, the intercellular interaction is performed by Delta–Notch system (Horikawa et al., 2006; Jiang et al., 2000; Mara et al., 2007; Özbudak and Lewis, 2008; Riedel-Kruse et al., 2007).

In more anterior region of the pre-somitic mesoderm, we observed the "traveling wave" of clock gene expression; the area of high expression moves from posterior to anterior direction (Fig. 1a). The speed of movement decreases gradually and the area of high expression becomes narrower as the wave moves. Such a traveling wave results from that the phase of oscillation within each cell changes with the location along the anterior–posterior axis. The anterior–posterior gradient of Fgf protein in which its concentration is the highest at the posterior end and decreases toward anterior direction (Dubrulle and Pourquié, 2004; Dubrulle et al., 2001; Sawada et al., 2001) may play an important role for the formation of traveling wave of gene expression. The disruption of Fgf gradient results in the wave patterns different from the wild type in zebrafish (Sawada et al., 2001). In addition to this a gradient of retinoic acid with opposite direction is observed in the pre-somitic mesoderm. Retinoic acid pathway is known to interact with Fgf pathway through mutual inhibition (Diez del Corral et al., 2003; Moreno and Kintner, 2004).

Modeling of the segmentation process of vertebrates was started by Cooke and Zeeman (1976) who proposed verbally that spatially periodic pattern of the somite can be formed by cyclic device within the pre-somitic mesoderm cells combined with cell fate determination moving at a constant rate to posterior direction, the latter being controlled by changing spatial pattern of a morphogen. Baker et al. (2006) analyzed this idea mathematically. Collier et al. (2000) discussed the possible relationship between the oscillating cell state and the cell cycle. Meinhardt (1982, 1986) discussed an alternative model based on the reaction–diffusion process. Kerszberg and Wolpert (2000) postulated that cells in the tail bud show oscillatory state, and that each pre-somitic mesoderm cell remembers its phase when it leaves the tail bud region. These models do not consider segmentation

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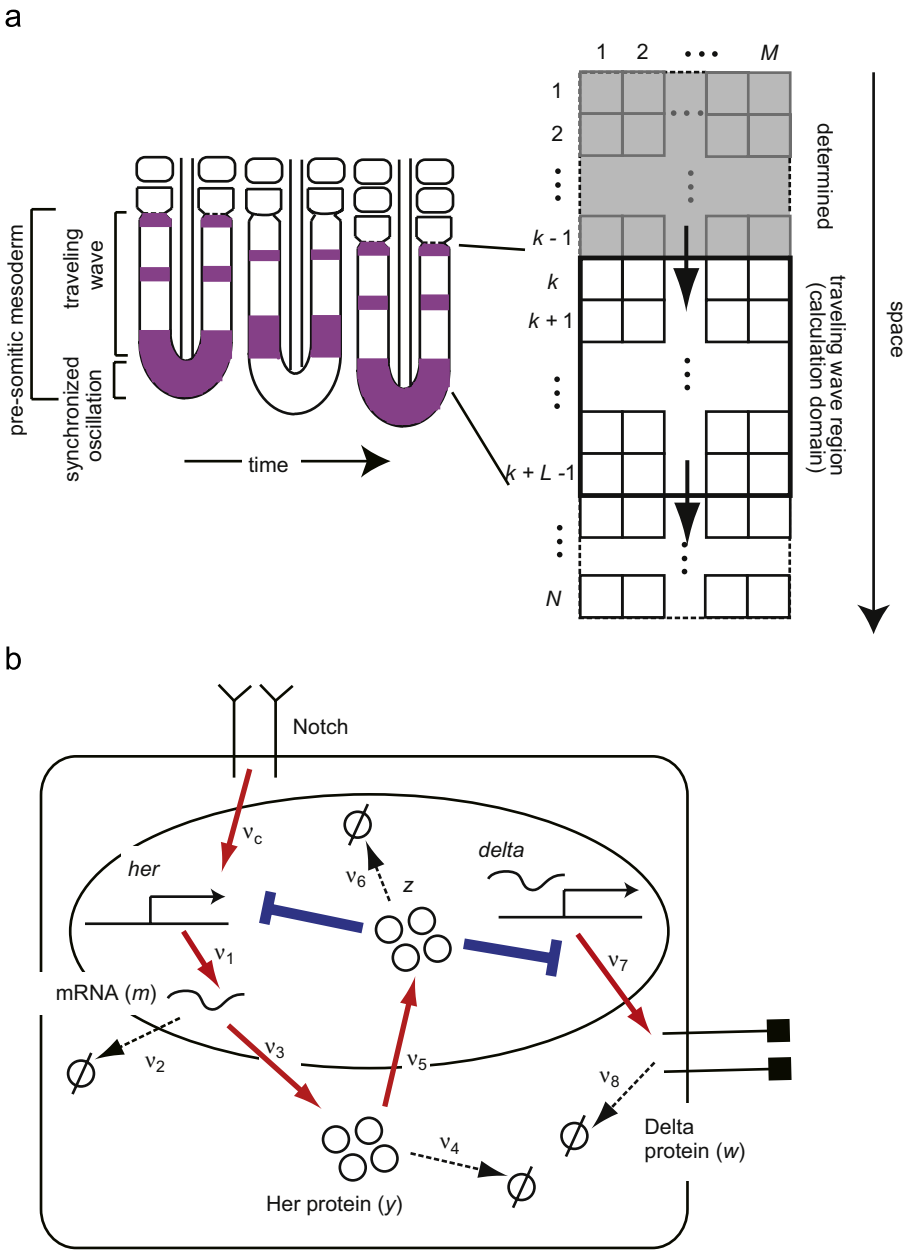

Fig. 1. (a) Expression pattern of *her* gene in the pre-somitic mesoderm in zebrafish and the moving domain of calculation. A rectangular area of two-dimensional lattice is divided into three regions: determined (shaded), the traveling wave region (framed) and the space posterior to the traveling wave region. Dynamics of gene expressions occurs in the traveling wave region only. It shifts posteriorly (as indicated by arrows) when the embryo elongates. (b) Negative feedback regulation of *her* gene within a cell and the cell–cell interaction between neighboring cells through Delta–Notch signal. The decay of mRNA and proteins is denoted by an arrow leading to symbol ∅.

clock genes, such as *her* (zebrafish), *hairy* (chick) or *hes* (mouse), explicitly.

Lewis (2003) examined the kinetics of *her* gene within each cell, in which negative feedback with time delay in the gene regulation is considered as a mechanism for generating the oscillatory expression of it. Lewis (2003) also showed that cell–cell interaction via Delta–Notch signal is able to produce synchronized oscillation of *her* gene expression between two cells. Horikawa et al. (2006) showed that the Lewis's model reproduces an experimental observation that cells constantly expressing Delta protein accelerate *her* oscillation in adjacent cells. Masamizu et al. (2006) and Tiedemann et al. (2007) also observed synchronized oscillation in a model for *hes* gene expression in mouse somitogenesis. Unlike Horikawa et al. (2006), Tiedemann et al. considered kinetics of *hes* mRNA, Hes protein in cytoplasm, and that in nucleus without explicit time-delay steps. Oscillatory expression of other clock genes in mouse such as *lunatic fringe* and *axin2* was also studied mathematically (Goldbeter and Pourquiè, 2008; Rodríguez-González et al., 2007). Santillán and Mackey (2008) modeled the stop of oscillatory expression of segmentation clock genes at the anterior end of the pre-somitic mesoderm by considering an interaction between Notch and Fgf/Wnt pathways.

Kærn et al. (2000) and Jaeger and Goodwin (2001) modeled the traveling wave patterns observed in the pre-somitic mesoderm by assuming that the gene expression level is a sinusoidal function of time. They assumed that the period of the segmentation clock increases as cells traverse the pre-somitic mesoderm. Cinquin (2007) considered the dimerization process of *her* 1/7 and *her* 13.2, and showed that the graded distribution of *her* 13.2 can