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Can tissue surface tension drive somite formation?

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Abstract

The prevailing model of somitogenesis supposes that the presomitic mesoderm is segmented into somites by a clock and wavefront mechanism. During segmentation, mesenchymal cells undergo compaction, followed by a detachment of the presumptive somite from the rest of the presomitic mesoderm and the subsequent morphological changes leading to rounded somites. We investigate the possibility that minimization of tissue surface tension drives the somite sculpting processes. Given the time in which somite formation occurs and the high bulk viscosities of tissues, we find that only small changes in shape and form of tissue typically occur through cell movement driven by tissue surface tension. This is particularly true for somitogenesis in the zebrafish. Hence it is unlikely that such processes are the sole and major driving force behind somite formation. We propose a simple chemotactic mechanism that together with heightened adhesion can account for the morphological changes in the time allotted for somite formation.

Keywords: Somitogenesis; Somite morphogenesis; Mechanical forces; Differential adhesion; Chemotaxis

Introduction

The generation of a periodic pattern of segments, known as somites, along the anterior–posterior axis of vertebrate embryos is one of the major unresolved problems in developmental biology (Schnell et al., 2002). Later in development, somites govern the segmental organization of peripheral spinal nerves, vertebrae, axial muscles, and the metameric distribution of blood vessels (Stickney et al., 2000; Stockdale et al., 2000).

A large number of theoretical models have been proposed (for a review, see Schnell and Maini, 2000; Baker et al., 2003), including the clock and wavefront model (Cooke and Zeeman, 1976; Dubrulle et al., 2001; Baker et al., 2006), the reaction–diffusion model (Meinhardt, 1986), the cell-cycle model (Stern et al., 1988; Primmett et al., 1989; Collier et al., 2000), and the clock and induction model (Schnell and Maini, 2000). Each of these models captures certain essential features of the underlying biology but fails to satisfactorily explain a number of other observations. The clock and wavefront model proposed by Pourquié and co-workers (Dubrulle and Pourquié, 2002; Pourquié, 2004) incorporates several well-known aspects of somitogenesis better than most models (Baker et al., 2006).

All present models share one common property: they predict that the presomitic mesoderm (PSM) is periodically segmented into tissue blocks which coalesce to form somites. However, the actual process of somite formation – how a somite pulls apart from the PSM and the ensuing morphological changes – are not well understood. In fact, they have not been the subject of modeling to date. All the models above are formalisms of somite specification not somite formation. The only mathematical model attempting to describe the bulk movement of somitic cells to form a somite is by Schnell et al. (2002). The major drawback of this model is that it does not take into account the intercellular mechanical forces involved in the process of somite formation. As a consequence, it cannot account for the morphological changes observed in somite formation.

The anterior portion of the PSM is the site of the forming somite; we shall refer to this as s_0. Cells in s_0 condense into somites by undergoing changes in their adhesive and migratory properties (Gossler and Hrabé de Angelis, 1998). These mechano-physical changes are brought about by an intricate pattern of gene activity and protein expression, a topic which is

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currently the subject of extensive research. Presently there are thought to be at least two distinct types of gene-driven processes that can individually or cooperatively lead to somite condensation: (i) differential expression of cell adhesion molecules and (ii) bidirectional activation of Eph receptors and ephrin-B proteins.

The differential expression of cell adhesion molecules is frequently associated with the development of organized patterns in embryogenesis (Takeichi, 1991; Gumbiner, 1996). For example, in the avian and mouse embryos somite formation is preceded by compaction of the s_0 region (i.e. a reduction of the intercellular spaces between cells) and the simultaneous heightened expression of two types of cadherin molecules, N-CAM and N-cadherin (Duband et al., 1987; Kimura et al., 1995). These adhesion molecules are also expressed in the rest of the PSM but at reduced levels when compared to that in the s_0 region. In mice somitogenesis (Kimura et al., 1995), it is found that cadherin-11 is strictly correlated with s_0 and is not expressed in other parts of the PSM.

In the past few years, it has been suggested that Eph/Ephrin signaling is as well required for the development of inter-somitic boundaries and the subsequent epithelization process (Durbin et al., 1998). This signaling pathway was also found to be responsible for boundary formation in the developing hindbrain (Mellitzer et al., 1999; Xu et al., 2000). In particular, it is observed that somite formation is accompanied by the differential expression of ephrin-B2 and EphA4 at the interface of the s_0 region and the rest of the PSM (Bergemann et al., 1995; Nieto et al., 1992). The current experimental evidence shows that Eph/Ephrin signaling also regulates the mesenchymal-to-epithelial transition of the PSM during somitogenesis (Barrios et al., 2003). The bidirectional signaling between the Eph and ephrin proteins mediates a contact-dependent repulsive mechanism that may aid in the separation of the two cell populations in the PSM and the s_0 region.

Though the genetic patterns underlying somite formation have been extensively studied during the last 10 years, it is not clear how these molecular patterns lead to the physico-mechanical processes responsible for sculpting a somite. In this article we present a study of how the coupling of molecular-level and cell-level processes may lead to somite formation. Our model suggests that independent of the actual molecular-level mechanism at play, the rounding typically exhibited by a somite during the time of its formation is unlikely to be solely accounted for by a minimization of tissue surface tension. We suggest another mechanism based on chemotaxis which together with heightened adhesion and Eph/ephrin signaling may explain the observed morphological changes during somitogenesis.

The viscous liquid model of tissue dynamics

As previously mentioned, cells in the s_0 region express various cadherins at the time of somite formation. Thus, cell–cell adhesion in this region becomes particularly strong compared to the adjoining PSM. At the same time, the differential expression of Eph and ephrin also occurs across the boundary separating the forming s_0 region and the PSM. It is indeed possible that these two seemingly different mechanisms do not act separately but rather are related or co-dependent on each other. For example, it has been found that Eph/ehprin signaling in certain neuronal processes leads to de-adhesion of cells at the boundaries by regulating cell adhesion molecules (Zisch et al., 1997).

The question we address in this work is how these molecular mechanisms lead to tissue re-arrangement culminating in somite formation. For this we need a model of tissue dynamics, one which captures the essential features observed experimentally. One of the most successful models is that originally proposed by Malcolm Steinberg, in which tissue is hypothesized to possess liquid-like properties (for example, see Steinberg, 1963). Among the theory's achievements is its ability to account for:

(i) how irregularly shaped tissue fragments have a tendency to round up towards a spherical shape,
(ii) the spontaneous sorting-out of experimentally intermixed embryonic cells of different types.

These two observations are easy to explain by analogy with liquids and their behavior. Molecules in the bulk of a liquid, being surrounded in all directions by many other molecules, experience zero net force. However, those molecules at the surface experience a net attractive force towards the center of the liquid. The potential energy associated with this net force (the surface tension) is minimized by minimizing the liquid's surface area, a feat accomplished by the liquid drop assuming a spherical shape. In the same way, cells at the outer surface of a tissue will experience a weak (though significant) net attractive force towards the center in a tissue composed of cells interacting via cell–cell adhesion forces. This leads to eventual rounding of the tissue to minimize its surface tension. Note that the spherical configuration also results in the maximization of intercellular adhesion. This explains (i) above.

Observation (ii) can be explained by analogy with the behavior of a two-phase liquid system. There are four possible equilibrium configurations for an initial configuration of cells, in which two different spherically shaped cell populations with different adhesion properties sit side by side. The determinants of the final configuration are the self-adhesion of cell type 1, the self-adhesion of cell type 2 and the cross-adhesion between cells of types 1 and 2. The possible configurations are as follows (Foty and Steinberg, 2004): (a) if there is no cross-adhesion then the two cell populations will form separate detached spheres (Fig. 1a); (b) a low degree of cross-adhesion weaker than either of the self-adhesion of the two cell types will result in a configuration in which the less cohesive population partially envelops the more cohesive population (Fig. 1b); (c) if the cross-adhesion is intermediate in strength then the less cohesive population will engulf the more cohesive population (Fig. 1c); (d) and if the cross-adhesion is equal to or greater than the average of the two population's self-adhesion then there will be intermixing (Fig. 1d).

Now let us apply the viscous liquid model of tissue dynamics to somitogenesis. We consider first the case where the separation of the s_0 region from the rest of the PSM occurs by Eph/ephrin bidirectional signaling. Ephrin-B2 is expressed in the posterior