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Trans-scale mechanotransductive cascade of biochemical and biomechanical patterning in embryonic development: the light side of the force

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Embryonic development is made of complex tissue shape changes and cell differentiation tissue patterning. Both types of morphogenetic processes, respectively biomechanical and biochemical in nature, were historically long considered as disconnected. Evidences of the biochemical patterning control of morphogenesis accumulated during the last 3 decades. Recently, new data revealed reversal mechanotransductive feedback demonstrating the strong coupling between embryonic biomechanical and biochemical patterning. Here we will review the findings of the emerging field of mechanotransduction in animal developmental biology and its most recent advancements. We will see how such mechanotransductive cascade of biochemical and mechanical patterning events ensures trans-scale direct cues of co-regulation of the microscopic biomolecular activities with the macroscopic morphological patterning. Mechanotransduction regulates many aspects of embryonic development including efficient collective cell behaviour, distant tissues morphogenesis coordination, and the robust coordination of tissue shape morphogenesis with differentiation.

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Introduction

Embryogenesis consists of the development of biomechanical morphology of tissues and biochemical cell differentiation patterns. In the developing embryo, the biomechanical and biochemical patterning were long considered as disconnected. The first was initially thought to be exclusively regulated by Newton's laws of Physics, with tissue growth as a major driving force [1], while the second was subsequently thought to be merely induced by the biochemical cascade based on the interactions between the biomolecules produced by the genome [2,3].

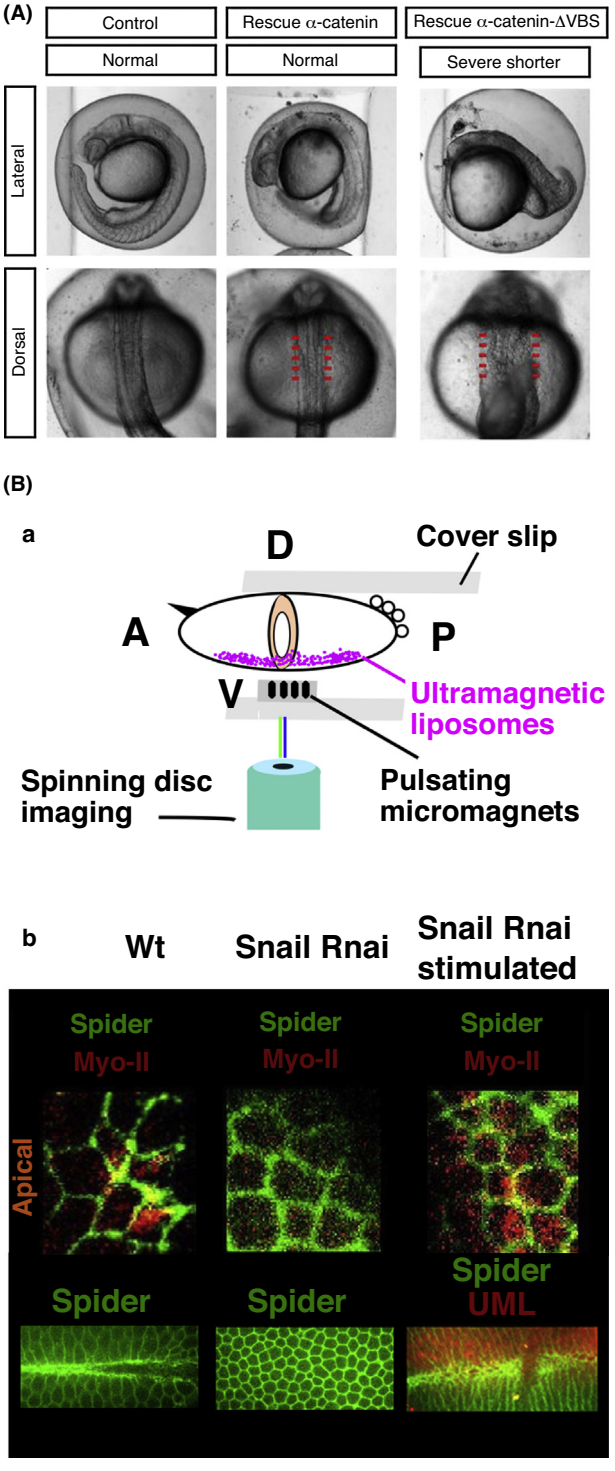
The biochemical regulation of embryonic mechanical patterning by the expression of master differentiation genes was discovered in the 90's, such as mesoderm invagination controlled by the expression of the genes *twist* and *snail* in *Drosophila melanogaster* embryos [4]. In addition, the antero-posterior patterning genes *bicoid*, *nanos* and *torso-like* are required for convergence-extension movements (C&E) at the onset of *Drosophila* embryo gastrulation [5]. Similarly, *Xwnt-5a* was suggested to be involved in C&E movements in Xenopus embryos [6] and *silberblick/wnt11* and *wnt5* were found to be necessary for proper C&E movements in zebrafish embryos [7].

The underlying molecular mechanisms downstream of this regulation are based on a genetic regulation of anisotropies in the intracellular concentration of a molecular motor: Myosin-II (Myo-II) [8]. For instance, the Twist and Snail proteins were found to be required for the medio-apical accumulation of Myo-II in *Drosophila* embryos. This acto-myosin meshwork constricts mesoderm cell apexes resulting in an apical shrinkage that triggers the mesoderm epithelium invagination [9].

These findings interestingly showed that embryo morphogenesis, that obeys the laws of Newtonian Physics, is the product of the physical conditions and of the biochemical patterns, that both introduce at a given developmental stage the internal forces that will determine the next stage.

Inversely, it has been shown in the 2000s that biochemical developmental patterns at a given stage can also be the product of the biomechanical patterns of the precedent stage through mechanotransduction processes. This introduces at given developmental stages, new biochemical signal inputs of mechanical origin. For instance, in gastrulating *Drosophila* embryos, mechanical strains developed by C&E induce beta-catenin (β-cat) signalling activation. This activation leads to Twist expression in the anterior endoderm, and is vitally involved in functional anterior mid-gut cell differentiation at larvae stage

Figure 1



(A) Defect of embryonic convergent-extension morphogenesis development during late epiboly somitogenesis, in the *ctnna1* E-α-catenin mutant rescued with the E-α-catenin ΔVBS lacking the mechanosensitive Vinculin binding site, compared to rescued with the wild-type E-α-catenin. **(B-a)** Quantitative mimicking of soft Sna-dependent apex pulsations in *sna*-defective embryos lacking pulsations (here *sna* RNAi, as well as *sna* and *halo sna* mutants –not shown) by magnetic forces generated with pulsatile micro-magnets on the order of the cell size applied on the mesoderm cells injected with ultra-magnetic liposomes, *in vivo*, **(b)** rescues the apical accumulation of Myo-II and of the mesoderm invagination from *sna*-defective embryos lacking apical stabilisation of Myo-II and mesoderm invagination (ventral views).

[10,11]. Similarly, during bone development in mouse embryos, *sox9* is expressed downstream of β-cat mechanical activation in response to muscle spontaneous activity to prevent bone differentiation in joints [12].

Here we will review the findings and most recent advances in the field reporting the existence of such mechanotransductive cues in animal embryonic development *in vivo*. We will focus on the mechanotransductive trigger of active morphogenetic biomechanical patterning, and on cell biochemical differentiation and specification patterning. We will describe the physiological functions of such coupling between the developmental biochemical patterning cascade and biomechanical shape development. Based on this trans-scale deterministic co-regulation of molecular activities with macroscopic properties, we will present how long-range rapid mechanotransductive cell–cell interactions generate either collective cell behaviour or embryonic morphogenetic movement coordination. We will additionally discuss how it engenders robust coordination between biochemical and biomechanical morphogenesis during embryonic development.

The mechanical trigger of Myo-II dependent active biomechanical morphogenesis

Myo-II protein is the molecular motor driving forces in embryonic active morphogenetic movements. Its mechanosensitive behaviour was initially found in cell culture [13]. *In vivo*, a simple micro-pipet aspiration of *Drosophila* embryos ectoderm increases the junctional concentration of Myo-II, suggesting a re-enforcement of junctions. Myo-II concentration also increases in ectoderm tissue in response to the C&E morphogenetic movements of gastrulation in *Drosophila* embryos [14]. In addition to re-enforcing tissue resistance to deformation, tension also stabilizes Myo-II at the purse-string caused by a wound during *Drosophila* embryogenesis [15]. The purse string tension increases and generates the wound closure.

The generalisation of such mechanically induced re-enforcement of junctions and of tissue integrity in response to embryonic morphogenetic movements was recently observed in early zebrafish embryos. In mutants with central domain-defective α-catenin, a domain known to be mechanosensitive in cell culture, the mechanical strains due to gastrulation led to C&E and embryo elongation defects [16•] (Figure 1A). In cell