ensures vigilance by scanning for both danger and strangers. ■

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Developmental biology

# Twisting the body into shape

Ian C. Scott and Didier Y. R. Stainier

Molecular signals are not the only forces that pattern and shape the developing embryo. Mechanical stresses sensed by cells also seem to be involved in creating the body plan.

Embryogenesis — the process by which a single cell gives rise to a multicellular organism — is one of nature's wonders. As cells increase in number, they engage in a series of complex movements that substantially alter their relative positions in the embryo. Patterning information that specifies anterior–posterior (head to tail) and dorsal–ventral (back to front) orientation is superimposed on this cellular framework, leading to the development of the early body plan. Many of the molecular signals that convey this patterning information have been identified. Now, writing in *Current Biology*, Emmanuel Farge[1] provides evidence that the mechanical forces generated by cellular migration can also play a role in shaping the embryo.

During the early stages of embryogenesis, a ball of cells is transformed into a multilayered structure, as cells invaginate from the surface and move inwards. This process generates the three 'germ layers', which go on to form all the organs of the body. Subsequent migrations, and changes in the cells' shape and adhesive properties, further alter the embryo's form. As the cells are linked to an extracellular matrix, they are subjected to forces exerted both by their own movements and by those occurring in other regions of the embryo. Mechanical stresses have been shown to affect gene expression in several cell types, most notably those lining the blood vessels[2]. So could the forces resulting from widespread cellular movements during embryogenesis affect the expression of the developmental genes required to set up the embryo's body plan?

To explore this possibility, Farge[1] mechanically compressed embryos of the fruitfly *Drosophila*, and then examined the expression of specific developmental genes. A gene called *twist* — involved in dorsal–ventral patterning[3] — is normally expressed only in the ventral region of the embryo, but Farge found that, within eight minutes of compression, *twist* expression had spread to encompass the entire embryo. Intriguingly, embryos in which the dorsal–ventral patterning system had been eliminated genetically also showed this expanded pattern of *twist* expression when compressed. So these results suggested that a pathway that is responsive to mechanical stress could affect patterning in the embryo.

But how is mechanical force translated into a change in gene expression? One protein that might couple these events is β-catenin, which is involved in both cell adhesion and gene activation[4]. Indeed, Farge found that compressing the embryo induced β-catenin to move into the cell nucleus — the site of gene activation. And inhibiting β-catenin, either by mutation or by overproducing proteins that interfere with β-catenin's gene-activating function, suppressed the stress-induced expression of *twist*.

So it seems that, through β-catenin, mechanical forces applied to the developing embryo can indeed affect the expression of developmental genes. But these experiments involved an artificial, external compression that does not occur during embryogenesis. To determine whether mechanical stresses inside the embryo contribute to its patterning, Farge examined a group of cells that are fated to form the most anterior portion of the digestive tract, called the stomodeum. He chose these cells because they lie between tissues that undergo extensive movements during embryogenesis: the posterior mesoderm, which lengthens and pushes on the anterior part of the embryo, and the invaginating anterior mesoderm and foregut. Farge found that as these tissues moved, the shape of the stomodeal precursor cells seemed to become compressed, and this compression coincided with increasing *twist* expression. Furthermore, as seen in the mechanically compressed embryos, the increase in *twist* expression required β-catenin activity in the nucleus.

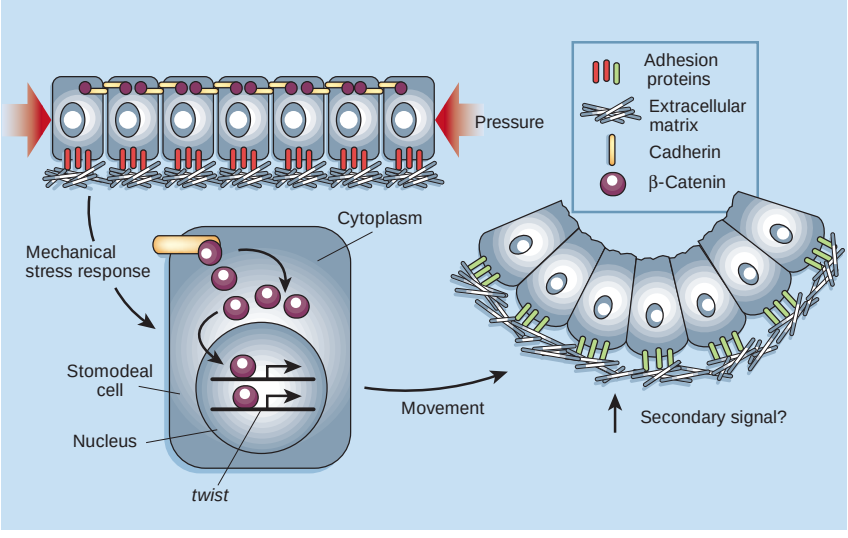


Figure 1 **The mechanics of shaping the digestive tract. New work by Farge[1] shows that mechanical compression of stomodeal precursor cells (which will form the part of the digestive tract called the stomodeum) can affect the expression of the *twist* gene. Pressure causes the β-catenin protein to move from the cell membrane (where it associates with cadherin) to the cytoplasm, increasing its concentration there. This movement in turn allows β-catenin to accumulate in the nucleus, where it activates *twist* and probably other developmental genes. *twist* is required for the invagination and development of the stomodeum. Possible 'downstream' responses may include changes in the contacts made between cell adhesion molecules and the extracellular matrix, facilitating invagination. The reaction to mechanical stress might also be 'permissive', allowing the stomodeal cells to interpret a secondary signal originating from surrounding tissues.**

Was the increase in *twist* expression in the stomodeal precursor cells really caused by movements of the surrounding tissues, or was it just a coincidence? To answer this question, Farge disrupted the forces exerted by the lengthening posterior mesoderm, either by inhibiting the lengthening itself or by eliminating the cells that link this tissue to the stomodeal precursor cells. In both cases, the stomodeal precursors no longer seemed to be compressed and showed no increase in *twist* expression. But, dramatically, when Farge compressed these cells using a metal probe, *twist* expression was activated. As this gene is known to be required for the stomodeum to invaginate and assume its normal shape[5], it now seems that mechanical stress, through the activation of *twist*, might directly regulate the development of this tissue (Fig. 1).

The effect of developmental genes on tissue movements during embryogenesis is being studied intensely. Farge's work shows that the mechanical forces generated by these movements can in turn regulate the expression of developmental genes. These forces have not been studied in detail and closer scrutiny is warranted[6]. For example, it will be interesting to investigate whether the stress-response pathway exists in other developmental contexts, such as the looping of the heart and gut tubes, where mechanical forces are probably involved. Another question is whether cells sense mechanical forces differently according to the nature of their contacts with the extracellular matrix. Some adult tissues may also experience mechanical stress — such as pressure from the growth of a tumour — so it will also be important to investigate how these stresses are involved in disease.

Current interpretations of how some genes function may also have to be revised in the light of whether or not they influence the generation of mechanical force, or the response to it. For example, it was previously known that β-catenin moves to the nucleus as a result of intracellular signalling triggered by the Wnt protein, but Farge has now shown that it can also relocate in response to mechanical stress. In the absence of either stimulus, β-catenin is found in two locations in the cell — near the cell surface, where mechanical forces could be sensed, and in the cytoplasm. So β-catenin function might have been co-opted to respond to two different stimuli.

The new study[1] prompts many other questions. How are mechanical signals transduced in other tissues? Is β-catenin a key player in all cell types? What targets other than *twist* are regulated? As Farge showed, artificial pressure can trigger β-catenin to move to the nucleus of stomodeal precursors and activate *twist*. Is this response sufficient to induce the invaginations required for the stomodeum to develop? Alternatively, is the response to pressure simply permissive, preparing the cells to respond to other inputs that induce movement? And what determines how a cell will move in response to these inputs? One thing is certain — examining the interplay between mechanical and molecular signals should open up new avenues in the study of many biological processes, including embryogenesis. ■

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Chemistry

# Mirrors in Flatland

Rasmita Raval

Many molecules exist in two mirror-image forms, which have different biological properties. A new way of creating solid chiral surfaces might make it easier to synthesize and purify only one of the mirror forms.

Chirality is widespread in nature and is fundamental to life. It arises from straightforward geometry — any object that lacks inverse symmetry can exist in two distinguishable mirror images, called enantiomers. For example, our hands are chiral: the right hand is an enantiomer of the left hand, and neither can be superimposed on the other by translation or rotation. At a molecular level, right-handed and left-handed compounds often have very different effects, so it is crucial for industry to produce pure enantiomeric forms. On page 490 of this issue, Switzer *et al.*[1] describe a way of creating a catalytically active chiral solid that could make the production of pure mirror images much easier.

Louis Pasteur introduced the concept of molecular chirality in 1848, when he observed that crystals of the chemical sodium ammonium tartrate tetrahydrate can form left-handed and right-handed structures[2]. Since then, chirality has been the cornerstone of several scientific advances, from the deduction that carbon atoms possess a tetrahedral arrangement of bonds[3,4], to the realization that terrestrial life-forms have evolved to make use of right-handed sugars and left-handed amino acids.

The inherent chirality of living systems dictates extraordinary specificity in the recognition of chiral molecules, so that a molecule and its mirror image, whether it is a pharmaceutical, an insecticide, a herbicide, a flavour or a fragrance, will almost always elicit different biological effects. This specificity presents a problem for the industrial synthesis of these compounds — chemists must control the three-dimensional spatial arrangements adopted by their products so that only the required enantiomer is produced. Underpinning this multibillion-pound global industry are chiral catalysts[5] that promote 'enantiospecific' reactions in which only one of the mirror images is formed. Most of these reactions are homogeneous — the reactants and the catalyst exist in the same phase (generally in solution). Heterogeneous catalysis, where the catalyst is in a different phase (usually solid) from the reactants, is a fledgling technology but is often a more active and robust system that enables the products of the reaction to be separated from the catalysts much more easily. Central to this new process is the ability to incorporate chirality in catalytic solids and surfaces.

So how are chiral surfaces formed on symmetric, achiral solids? Although prevalent in the living, organic world, chirality is rarely found in catalytically active inorganic materials and surfaces. But this property can be transmitted from organic molecules to inorganic systems in a number of ways[6–8]. For example, if organic 'right-handed' (*R*,*R*)-tartaric acid enantiomers are adsorbed onto the symmetric, achiral surface of solid copper, the tartaric acid molecules assemble into a chiral template on the copper surface. This exposes chiral channels within which the copper atoms are available to react with other molecules[6]. The entire assembly can assume the mirror image by adsorbing the 'left-handed' (*S*,*S*)-tartaric acid enantiomer instead (Fig. 1, overleaf).

As well as simply providing a template on a solid surface, adsorbed molecules can also induce the large-scale reorganization of metal surfaces to expose chiral facets. This, for example, is how the organic amino acid *S*-lysine transmits chirality to the surface atoms of solid copper[8]. And surface adsorption can also affect three-dimensional chirality[9,10] — symmetric calcite crystals can adopt asymmetric, chiral shapes when grown in the presence of enantiomers of the amino acid aspartic acid[10].