On the basis of the topochemical postulate, Schmidt's colleague Cohen formulated the concept of the reaction cavity (*10*, *11*). According to this concept, molecules in crystals can be visualized as existing in rigid, three-dimensional cavities formed by their nearest neighbors. As the central molecule reacts, its geometry changes within the cavity. Reactions that involve minor changes in reactant geometry are topochemically allowed, that is, they proceed without restriction from the cavity walls, whereas reactions with transition state geometries that do not fit within the cavity will be strongly disfavored.

The topochemical postulate and the reaction cavity concept have stood the test of time. Countless scientific studies, including the work of Irie *et al.* (*2*), attest to their validity. The photochromic cyclization reaction of **1** is a unimolecular process that involves very slight geometric changes from reactant to product—so much so that reactant and product can coexist happily in the same crystal lattice, and the reaction is of the relatively rare single crystal–to–single crystal variety (*12*).

Carrying out organic reactions in the crystalline state has one distinct advantage. It eliminates the need to dispose of large volumes of waste solvent once the reaction is complete, a not insignificant consideration in the current age of increased environmental awareness. There will always be a need to carry out organic chemical reactions in the liquid phase, not least because not all organic compounds form solids at convenient temperatures and pressures, but solid state organic chemistry represents a unique and rapidly growing interdisciplinary field with important practical applications in materials science and chemistry (*13*).

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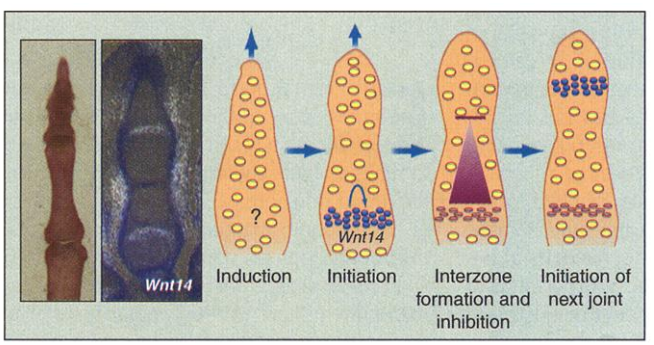
PERSPECTIVES: DEVELOPMENT

The Art of Making a Joint

François Spitz and Denis Duboule

During vertebrate evolution, the successful adaptation of limbs to a variety of ecological niches depended largely on the formation and correct positioning of synovial joints. These articulations between the long bones of our arms and legs enable our limbs to move smoothly—a fact that all of us, sooner or later, come to realize. Diseases of human synovial joints, such as rheumatoid arthritis, restrict movement and are debilitating. To design better therapeutic strategies for treating joints damaged through injury or disease, we need to understand not only how joints are made, but also what determines their exact spacing and reiteration. Several molecules that direct joint development have been identified, including a growth and differentiation factor, Gdf5, that is related to transforming growth factor–β (TGF-β) (*1*). Both mouse Gdf5 and its homolog CDMP1 in humans are mutated in syndromes where the arrangement of bones in the fingers and toes is abnormal (*2*, *3*). With the report by Hartmann and Tabin in a recent issue of *Cell* (*4*), another member can now be added to the meager cadre of proteins that direct joint development. These investigators show that Wnt14, a member of the Wnt family of signaling molecules, is a key player in the formation of synovial joints in the developing limbs of the chick embryo.

During limb development, long bones appear as continuous condensations of mesenchyme composed of prechondrogenic (cartilage precursor) cells. These mesenchyme condensations first form in the proximal region of the future limb, assembling into primordial tissue that will eventually differentiate into the long bones of the arm and leg (humerus and femur, respectively.) As the mesenchyme expands, it starts to branch, forming the bone primordia of the radius and ulna, or tibia and fibula. The distal regions of these bone primordia then branch further, laying down precursor tissue that will form the carpals and tarsals, metacarpals and metatarsals, and finally the phalanges of the fingers and toes (*5*, *6*). Within this continuous branching mesenchyme, the positions of the future joints are demarcated by areas of higher cell density called interzones (see the figure). Cells in the interzone begin to lose the properties of prechondrogenic cells: They become flattened and no longer make the typical extracellular matrix components of cartilage. The interzone becomes arranged into three layers: two areas of higher cell density that will form the articular cartilages of the joint, and a region in between of lower cell density where the cells eventually die, leaving behind the joint



Articulating joint formation. (Far left) A photograph of digit bones in the mouse skeleton illustrates how the articulations of digits rely upon the proper formation and positioning of synovial joints. **(Near left)** A developing embryonic chick limb (stage 33) contains an extending mesenchyme condensation (purple) bounded by two interzone areas (white stripes) that express the signaling molecule Wnt14. Future joints will form at the locations of the white stripes. **(Right)** The three right-hand panels illustrate a possible sequence of events during joint formation in the developing vertebrate embryo. An unknown inductive signal determines the position of the first interzone (question mark). Prechondrogenic cells in the mesenchyme condensation differentiate into interzone cells that produce Wnt14 (blue). This protein activates the expression of downstream genes encoding factors (red) that block the "joint forming" capacity of nearby prechondrogenic cells. The next interzone will form sufficiently far away from the first where the prechondrogenic cells are not affected by the inhibitory factors.

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cavity. Prechondrogenic cells surrounding the interzone form the joint capsule and the tendon attachments to adjacent muscle (*1*).

In their search for molecules directing the formation of long bones in the chick embryo, Hartmann and Tabin (*4*) realized that the pattern of Wnt14 expression implicated this signaling molecule in the segmentation of mesenchyme condensations. Wnt14 is expressed both in interzone cells located at the position of future joints, and in neighboring nonchondrogenic cells. Intriguingly, in the fully formed chick limb, Wnt14 is still expressed in joint synovial membrane and connective tissue. These observations prompted the authors to overexpress the *Wnt14* gene in prechondrogenic cells of distal mesenchyme in the chick limb bud.

Overexpression of *Wnt14* resulted in the formation of abnormal cartilage elements or the absence of cartilage altogether. This suggests that Wnt14 may instruct prechondrogenic cells to differentiate into something other than cartilage. Prechondrogenic cells overexpressing Wnt14 appeared to be morphologically similar to interzone cells—they produced large amounts of type III collagen (an essential component of joints) but very little chondromucin (found in cartilage) (*1*). This result implicates Wnt14 in the induction of joint formation (although true joints were not formed, possibly because of the variable amounts of Wnt14 produced in this rather artificial system).

A pivotal part for Wnt14 in joint development was substantiated by data from micromass cultures, which were prepared from embryonic chick limb (stage 22 to 23). Overexpression of Wnt14 in micromass cultures did not prevent the formation of pre-cartilage aggregates but did inhibit the differentiation of these aggregates into cartilage nodules. The presence of interzone-specific markers—such as Gdf5, autotaxin, and chordin—confirmed that Wnt14 was instructing prechondrogenic cells to become interzone cells. Thus, Wnt14 initiates joint formation, probably acting upstream of Gdf5, autotaxin, and chordin.

The investigators noticed that whenever Wnt14 induced the formation of an interzone in one place, interzone formation at a nearby location was blocked. Therefore, Wnt14 may also be essential for the correct spacing of joints and, in turn, for the formation of the correct number of bones in the limb skeleton. The capacity to form joints may be an intrinsic property of all prechondrogenic cells in mesenchyme condensations. External guidance cues may direct prechondrogenic cells in the proximal region of mesenchyme to form an interzone. Release of inhibitory molecules by interzone cells would then prevent the formation of a second interzone too close to the first. The second interzone would then be formed only by prechondrogenic cells that were sufficiently far away to be unaffected by the inhibitory factors. This sequence of events may be correct: Interzone cells produce chordin, an inhibitor of bone morphogenetic proteins (BMPs), whereas cells surrounding mesenchyme condensations produce BMPs, which are known to promote joint formation. Although robust evidence is still lacking, it is intriguing that treatment of chick limb buds with noggin (another BMP inhibitor) reduces the number of phalanges (*7*).

In any case, if the formation of one joint is necessary to determine the position of the next, induction of the first interzone still needs to be explained. The first joint forms at the initial branching point of the mesenchyme condensation (*6*). From an evolutionary perspective, it is logical that joint formation should be linked to the segmentation of bone primordia—the branching of one bone into two is of no benefit if it is not accompanied by introduction of an articulation. There is little doubt that joint formation is intimately linked to the spatiotemporal organization of mesenchyme condensations. Wnt14 may well turn out to be a key player in both bone segmentation and joint formation.

Finally, the continued production of Wnt14 by cells in the synovial membranes and capsules of mature joints supports the notion that Wnt signaling is involved in the maintenance of adult synovial joints. Messenger RNA transcripts for some Wnt molecules and their target genes are up-regulated in the synovial joint cells of patients with rheumatoid arthritis (*8*). Engineering mice with mutations in different Wnts should reveal whether the Wnt signaling pathway is necessary for the maintenance of joint integrity. If it is, then members of the Wnt family may provide new therapeutic targets for treating synovial joint diseases.

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PERSPECTIVES: GEOPHYSICS

When the Compass Stopped Reversing Its Poles

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Earth's magnetic field reverses a few times every million years at random intervals, as a result of positive feedbacks to magnetohydrodynamic instabilities within the liquid iron core (*1*). Occasionally, however, the dynamo mechanism in Earth's liquid iron core stops its dance of random dipole field reversals and for 30 to 50 million years maintains either "normal" polarity (like today) or the reversed state (in which a compass would point south). At least two such superchron periods are known in the recent geological past. Between 118 and 83 million years ago (Ma) (the Cretaceous superchron), the field maintained constant normal polarity, and it remained reversed from 312 to 262 Ma. Why did the random dipolar reversal suddenly stop, and what made the stochastic dance start again?

To answer this question, we require accurate data of geomagnetic field behavior during a superchron, so as to devise and test models of geomagnetic dynamo behavior that could cause it. On page 1779 of this issue, Tarduno *et al.* (*2*) report the latest in a series of innovative attempts to accurately determine the magnitude of the magnetic field at Earth's surface and the virtual dipole moment (VDM) at Earth's center that is responsible for it before, during, and after the Cretaceous superchron (*3–5*). Unlike low values found by previous authors, however, Tarduno *et al.* find that during the superchron, the time-averaged VDM was 12×10^{22} A/m^2—twice as high as the average for the past 160 Ma (*4*) and 50% higher than today.

Obtaining a truly accurate datum that is not contaminated by local effects unrelated to the global dipole field is a real tour de force. Tarduno *et al.* used a multistep polishing and etching method to extract 149 single crystals of plagioclase feldspar from eight independent lava flows that erupted at different times between 113 and 115 Ma. Other researchers have previously performed paleomagnetic and rock magnetic studies at the

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