This Week's Citation Classic®

Trelstad R L, Hay E D & Revel J-P. Cell contact during early morphogenesis in the chick embryo. *Develop. Biol.* 16:78-106, 1967.
[Department of Anatomy, Harvard Medical School, Boston, MA]

Morphogenesis requires translocations of cellular position and transformations of cellular phenotype. In the early chick the primary mesenchyme derives from the epiblast. During this epithelial-mesenchymal transformation, the emigrating cells retain and maintain an aligned position in respect to the primitive streak. Close contacts between cells with apparent specializations at the plasmalemma were described between cells of similar and dissimilar phenotype. [The *SCI*® indicates that this paper has been cited in over 180 publications.]

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July 13, 1987

When I was at Columbia University as an undergraduate in the early 1960s, Lester Barth, Frances Ryan, and Teru Hayashi provoked in me a lifelong curiosity about the generation of three-dimensional form in the embryo. As a medical student at Harvard University in the mid-1960s, I had the opportunity to work with Elizabeth D. Hay and Jean-Paul Revel in the Department of Anatomy, then chaired by Don Fawcett.

During the summers and later, during a one-year leave of absence, I studied the organization of the chick embryo using both light and electron microscopy, paying particular attention to the early stages of the chick. Interest in these early stages was spawned, in part, by reading *Cytology and Evolution*[1] by E.N. Willmer; in this book he classified all cells from metazoans into amoebocytes, mechanocytes, and epitheliocytes. Possible transformations among these cell types and attention to cell polarity, two major themes in Willmer's work, were in my mind's eye as I pursued the work that resulted in this highly cited paper.

One of the most exciting aspects of my studies of the early embryo was the recognition that cells, both mesenchymal and epithelial, were designed to behave as very polarized entities. I was able to follow cells from the epithelial epiblast to the primary mesenchyme and then watch this mesenchyme align to form the epithelial sheets of the visceral and parietal mesoderm and spherical epithelial somites; I could then follow the change of the somite epithelium back to a mesenchyme to become chondrocytes. While some may challenge the active voice of the previous sentence, the attention to cell positions and postures in static micrographs coupled with an *a priori* assumption that "order builds on order" helped recreate what seems to be an accurate description of these early stages of development. It also made me aware that epithelial and mesenchymal states were interchangeable; in fact, epithelial-mesenchymal transformations[2] and cell polarity[3,4] are a recurrent theme in my later studies.

Contemporaneous work in 1963 by Jud D. Sheridan in the laboratory of David Potter and Ed Furshpan at Harvard Medical School indicated that the early cells in the chick gastrula were electrically coupled.[5] I recall an afternoon with Sheridan, Hay, Revel, Furshpan, and Potter in which we pored over my recent electron micrographs of the early embryo. We wondered if the focal points of contact between the epithelium and mesenchyme were possible sites of ion flow between the cells.[6] Subsequent work by Revel and M.J. Karnovsky shifted focus to the gap junction, at that time an unknown but soon to be described contact specialization.[7]

Efforts to improve the fixation of the early chick embryo led to countless hours in the cold room with an infusion apparatus in which I perfused osmium in various combinations and permutations with buffers, salts, and additives. From 1961 to 1965 the "quality" images required in Fawcett's department were generated by "mass action" by fixing countless embryos, cutting countless sections, and taking countless micrographs. The advent of glutaraldehyde allowed me to obtain in 1966 even better and more consistent images, and such were the foundation of the manuscript.

The paper was written at the end of my last year at medical school and the first year of an internship in pathology at the Massachusetts General Hospital. The drafts that were submitted to Hay and Revel were returned with a luster unattributable to the first author. The final version was ultimately much of the red ink.

The paper was thus the typical marriage of a student's labor and enthusiasm with a mentor's patience and experience. While the paper is often cited for demonstrating contacts between epithelium and mesenchyme, it contains the germ of an idea that carries forward into current thinking, *viz.*, the polarity of individual cells, both epithelial and mesenchymal, and the likelihood that some "rules" operate on these anisotropic elements to generate metazoan form. That obsession has only gotten broader and better.[8]

1. **Willmer E N.** *Cytology and evolution.* London: Academic Press, 1960. 430 p.
2. **Trelstad R L, Hayashi A, Hayashi K & Donahoe P K.** The epithelial-mesenchymal interface of the male rat Mullerian duct: loss of basement membrane integrity and ductal regression. *Develop. Biol.* 92:27-40, 1982.
3. **Trelstad R L & Birk D E.** Cell polarity and collagen fibrillogenesis during morphogenesis of the tendon and corneal stroma in the chick. (Trelstad R L, ed.) *The role of the extracellular matrix in development.* New York: Liss, 1984. p. 513-43.
4. **Holmes L B & Trelstad R L.** Patterns of cell polarity in the developing mouse limb. *Develop. Biol.* 59:164-73, 1977.
5. **Sheridan J D.** Electrophysiological study of special connections between cells in the early chick embryo. *J. Cell Biol.* 31:C1-C5, 1966. (Cited 65 times.)
6. **Trelstad R L, Revel J-P & Hay E D.** Tight junctions between cells in the early chick embryo as visualized with the electron microscope. *J. Cell Biol.* 31:C6-C10, 1966. (Cited 80 times.)
7. **Revel J-P & Karnovsky M J.** Hexagonal array of subunits in intercellular junctions of the mouse heart and liver. *J. Cell Biol.* 33:C7-C12, 1967. (Cited 960 times.) [See also: **Revel J-P.** Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 1: cell biology.* Philadelphia: ISI Press, 1986. p. 21.]
8. **Trelstad R L, Hayashi M, Hayashi K & Birk D E.** Fibrils, fibonacci and fractals: searching for rules and rulers of morphogenesis in the orthogonal stroma of the chick cornea. (Hilfer R & Sheffield J, eds.) *Ocular development.* (In press.)

CC/LS 1-17