One Signal, Two Body Axes

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A single signaling molecule, a homolog of transforming growth factor–α (TGF-α) encoded by the *gurken* gene, initiates polarity along both the dorsal-ventral and anterior-posterior body axes during *Drosophila* oogenesis, as reported in two recent articles—one from the laboratory of D. St. Johnston and one from T. Schüpbach (*1*, *2*). First, in midoogenesis, the posteriorly positioned nucleus of the oocyte sends the Gurken signal to the nearest follicle cells, instructing them to take on a posterior identity. Second, at a slightly later stage, the oocyte nucleus moves to an anterior corner of the oocyte and sends a second Gurken signal to the adjacent follicle cells, which acquire a dorsal identity (see figure). The asymmetries in the follicle cells then control the final polarity of the oocyte and embryo.

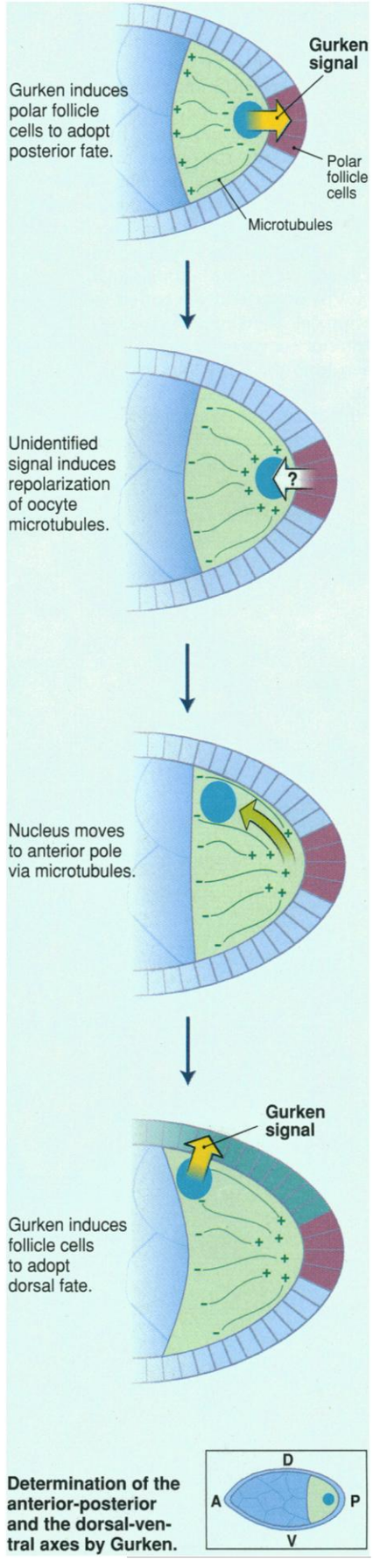
Signaling between the oocyte and the somatic follicle cells has been known to be a key component of the initiation of the dorsal-ventral pattern for nearly a decade, since Schüpbach showed, using genetic mosaics, that dorsal follicle cell fate and the dorsal-ventral pattern of the *Drosophila* embryo depend on the activity of the *Drosophila* epidermal growth factor (EGF) receptor gene *torpedo* in the follicle cells (*3*). The key role of the *gurken* gene, which is required in the germ line cells, was also first described by the Schüpbach lab. The *gurken* gene, like *torpedo*, is required for dorsal follicle cell fate and the embryonic dorsal-ventral pattern; it encodes a TGF-α–like protein that could directly activate the *torpedo* EGF receptor in the follicle cells (*4*).

Anterior-posterior patterning depends on cytoplasmic localization of *bicoid* RNA at the anterior pole and *oskar* RNA at the posterior pole of the oocyte. When first described, the localization of these RNAs seemed to be intrinsic to the germ line and not depend on any intercellular signaling. The two recent articles are the culmination of a set of experiments from several labs showing that the localization of the *bicoid* and *oskar* RNAs is the outcome of reciprocal signaling, first from the oocyte to the follicle cells, and then back from the follicle cells to the oocyte.

The first indication that the follicle cells are important in anterior-posterior polarity was that the proteins Notch and Delta are required in the follicle cells for proper localization of *bicoid* RNA (*5*). The next advances in understanding how the follicle cells might control *bicoid* RNA localization came from studies that revealed a relation between the follicle cells and the oocyte cytoskeleton. Theurkauf and his colleagues showed that at the time *bicoid* and *oskar* RNAs become localized, there is a dramatic reorganization of the microtubules in the oocyte (*6*). Early in oogenesis, microtubules are polarized with their minus ends in the oocyte and their plus ends in the anteriorly positioned nurse cells, thereby promoting transport of nutrients from the nurse cells to the oocyte by means of dynein-like motor proteins. At the time of the first anterior-posterior polarity within the oocyte, the microtubule organization changes, so that the plus ends of microtubules are at the posterior and the minus ends are at the anterior of the oocyte. A kinesin-β–galactosidase fusion protein localizes to the posterior of the oocyte at this crucial stage of oogenesis and provides a useful reagent to analyze the effects of mutations on the cytoskeletal polarity in the oocyte (*7*). Mutations in *gurken* and *torpedo*, as well as in *cornichon*, *Notch*, *Delta*, *protein kinase A*, and *spindle C*, all prevent the localization of kinesin-β–galactosidase to the posterior pole; instead, in these mutants the fusion protein is enriched in the middle of the oocyte. Thus, all these genes are required for the correct organization of microtubules in the oocyte at the time when anterior-posterior polarity is initiated. These mutations also cause mislocalization of *bicoid* and *oskar* RNAs, with *oskar* RNA mislocalizing to the middle of the oocyte and *bicoid* RNA to both poles of the oocyte.

Prior to the microtubule reorganization, Gurken protein is associated with the oocyte nucleus, which is situated at the posterior pole of the oocyte, and Torpedo is required in the adjacent follicle cells to receive the Gurken signal. Because *gurken* and *torpedo* are required for the oocyte microtubule reorganization, this signal from the oocyte to the follicle cells presumably activates a posterior-specific program in the polar follicle cells. The posterior polar follicle cells must then use an unknown molecule to signal back to the oocyte and somehow control the position of microtubule organizing centers within the oocyte.

As a consequence of the change in microtubule organization, the oocyte nucleus



Determination of the anterior-posterior and the dorsal-ventral axes by Gurken.

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moves along the plasma membrane toward the anterior of the oocyte. When the nucleus arrives at an anterior corner of the oocyte, it sends a Gurken signal to the adjacent follicle cells, thereby triggering them to acquire dorsal cell fates. In *gurken* and *torpedo* mutants, the oocyte nucleus associates with the plasma membrane, but because of the improper microtubule organization it does not move to the anterior of the oocyte reliably, which affects which follicle cells receive the dorsalizing signal.

Why does the ovary bother with all this reciprocal signaling? Signaling from the posterior oocyte nucleus to follicle cells and then from the same follicle cells back into the oocyte to control RNA localization seems rather baroque. Similarly for the dorsal-ventral axis, the Gurken signal triggers dorsal follicle cell fate which, through a set of poorly understood events, leads to the ventral activation of the extracellular protein Spätzle, which signals back into the embryo to control embryonic dorsal-ventral patterning (8). The answers to these questions will surely provide insight into how the initial polarities are turned into embryonic pattern. One clear result of the signaling events is a timing delay. This timing delay is particularly obvious for dorsal-ventral patterning, where the Gurken signal during oogenesis acts through intermediate steps to control events that happen after fertilization. Reciprocal signaling also provides the opportunity for spatial refinement steps that could use small initial asymmetries to create the gradients of information that direct early embryogenesis.

Why does *Drosophila* use a single molecule to initiate polarity in both of the body axes? Perhaps the ancestral embryo found that by moving the nucleus to different positions within the oocyte, the same signal sent at two separate times could define two body axes. It will be interesting to investigate the relations between the position of the oocyte nucleus and the body axes in other animals.

References

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