



Review

How signaling between cells can orient a mitotic spindle

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ABSTRACT

In multicellular animals, cell communication sometimes serves to orient the direction in which cells divide. Control of division orientation has been proposed to be critical for partitioning developmental determinants and for maintaining epithelial architecture. Surprisingly, there are few cases where we understand the mechanisms by which external cues, transmitted by intercellular signaling, specify the division orientation of animal cells. One would predict that cytosolic molecules or complexes exist that are capable of interpreting extrinsic cues, translating the positions of these cues into forces on microtubules of the mitotic spindle. In recent years, a key intracellular complex has been identified that is required for pulling forces on mitotic spindles in *Drosophila*, *Caenorhabditis elegans* and vertebrate systems. One member of this complex, a protein with tetratricopeptide repeat (TPR) and GoLoco ($G\alpha$ -binding) domains, has been found localized in positions that coincide with the positions of spindle-orienting extracellular cues. Do TPR–GoLoco proteins function as conserved, spatially regulated mediators of spindle orientation by intercellular signaling? Here, we review the relevant evidence among cases from diverse animal systems where this protein complex has been found to localize to specific cell–cell contacts and to be involved in orienting mitotic spindles.

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Introduction

Cell division orientation is an important part of development and tissue maintenance [1–6]. Abnormal placement of the division plane has been recognized to disrupt cell fate specification for over

30 years [7] and has more recently been proposed to contribute to defective morphogenesis [1,2,5] and cancer [8]. While cell shape has been shown to be one contributor to placement of cell division planes [9–12], recent discoveries have highlighted a role of cell signaling in spindle orientation.

Since the 1990s, it has become clear that extrinsic signals can determine the orientation in which certain cells divide. Manipulating the positions of cells and signals has revealed that the position from which an extrinsic signal is presented to a cell can determine the orientation of the cell division machinery [13–15]. These experiments make clear that extrinsic signals can function not just

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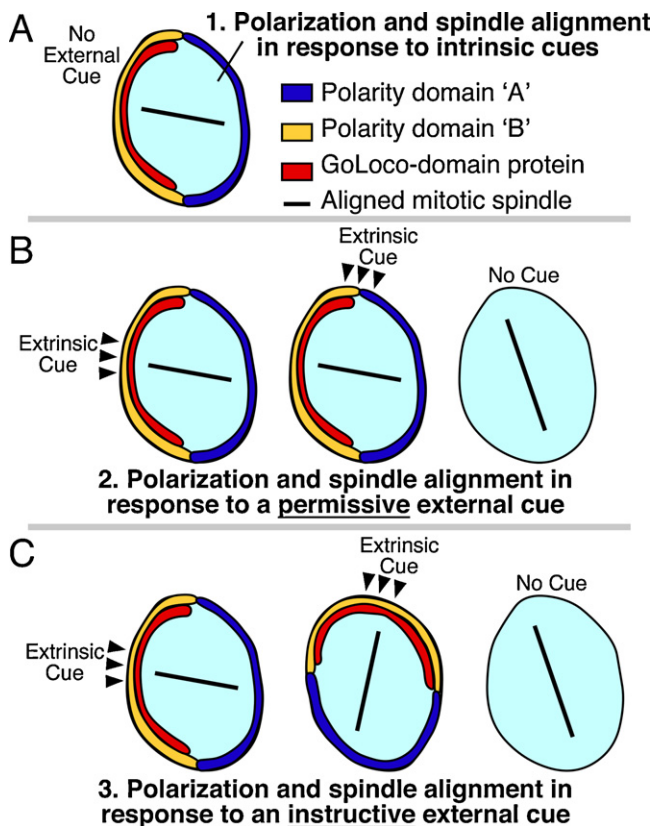


Fig. 1. Polarity establishment by intrinsic cues, permissive external cues, and instructive external cues. (A) Some cells align their mitotic spindles independent of external signaling cues. Polarity domains 'A' and 'B' are nonspecific and could represent 'Anterior' and 'Posterior' polarity, 'Apical' and 'Basal' polarity, 'Dorsal' and 'Ventral' polarity, etc, depending on the specific cell type. (B) Permissive external cues: some cells require an external cue (black arrowheads) for polarization and spindle alignment, but the position of that cue does not convey positional information to cell polarity: moving the cue has no effect on cell polarity or spindle orientation (middle). Absence of these cues leads to polarity defects and defects in spindle orientation (right). (C) Instructive external cues: some cells are polarized by instructive external cues (black arrowheads), where changing the position of the cue changes the orientation of polarity and division. Experimentally moving the position of an extrinsic cue differentiates between permissive (B) and instructive (C) functions in spindle orientation.

as simple switches that allow cells to respond to internal polarity (permissive cues), but instead can serve as important positional landmarks that determine the specific orientations of mitotic spindles (instructive cues) (Fig. 1): cells are telling their neighbors in which direction to divide.

Surprisingly, while studies of cell division orientation have been carried out for over a century [16], very little is known about how intercellular signaling leads to normal division orientation. In principle, for a cell to divide in an orientation determined by extrinsic signals, several events need to occur: (1) first, the cell needs to receive an external cue from a neighboring cell. This cue can come in multiple forms, such as a secreted molecule, like Wnt [14], or a transmembrane or adhesive molecule, such as cadherin [17]. (2) Second, the cell needs to interpret the external cue, translating its position into internal polarity. (3) Third, the internal polarity must be translated into forces on the cytoskeleton to set up a specified axis of division. (4) Lastly, the cell needs to divide. This can result in the partitioning of cell fate determinants [18], to one daughter cell.

1. Molecular transducers of positional information from intercellular signaling to spindle orientation

1.1. An example of the importance of intercellular communication for cell division orientation: the role of cadherin in the *Drosophila* germline

Cell–cell signaling regulates division orientation and cell fate in the male and female germline stem cells (GSCs) in *Drosophila*. GSCs in the *Drosophila* germline receive signals from cells within the stem cell niche, aligning the mitotic spindle of the stem cell perpendicular to the area of contact with the niche. These signals come in the form of bone morphogenetic protein (BMP) from cap cells and signals for Janus kinase–signal transducers and activators of transcription (JAK–STAT) signaling from the hub cells in the female and male germline respectively. Signaling between the hub or cap cells and the GSCs controls GSC renewal [19]. In both the male and female germlines, cadherin molecules localize at the boundary of cap or hub cells and the germline stem cells, are required to maintain stem cell adhesion within the niche, and are involved in stem cell polarization and spindle orientation [20,21]. Loss of E-cadherin in the male or female germlines results in loss of GSCs from the niche [20,22]. In the male germline, GSC spindle orientation may be determined partly by asymmetric inheritance of mother vs. daughter centrosomes: centrosomes are segregated asymmetrically, with the mother centrosome always remaining anchored to the contact with the niche [23]. The mother centrosome is likely anchored by a physical link between astral microtubules and E-cadherin-rich adherens junctions between the stem cell and the hub cells through an APC (adenomatous polyposis coli) protein [21,24]. In this system, it has not been shown whether E-cadherin and APC function as instructive cues for spindle orientation or whether this centrosome-anchoring phenomenon merely provides a permissive external cue to orient division in response to a separate cue. In the future, it would be interesting to determine whether GSC division is oriented by instructive or permissive cues from the hub, by experimentally repositioning the adherens junctions, possibly through cell manipulations, and assaying for re-establishment of centrosome anchoring and reorientation of the mitotic spindle of the stem cell in relation to the hub.

E-cadherin and APC have also been implicated in similar processes in other systems, namely the regulation of cell polarity [17,25], centrosome tethering [26], and mitotic division orientation [27]. This suggests that E-cadherin-mediated polarity is one key way in which cells communicate to regulate division orientation. (For a recent review on adhesion molecules regulating stem cell division, see [28].)

1.2. TPR–GoLoco proteins as candidate transducers of positional information from intercellular signaling to spindle orientation

In a wide range of animal systems, members of a conserved protein complex, the TPR–GoLoco complex, are important for regulating division orientation. These systems include *Caenorhabditis elegans* embryos [29–31], *Drosophila* neuroblasts and sensory organ precursors [15,32–35], a variety of vertebrate epithelia [36–40], mammalian neural progenitors [41–43], mammalian T-cells [44], and gastrulating zebrafish embryos [35]. This complex was discovered independently in *C. elegans* embryos, *Drosophila* neuroblasts, and cultured mammalian cells. In the mid-1990s, heterotrimeric G-proteins were implicated in cell division orientation in *C. elegans* embryos, as early as the one-cell stage [45]. $G\alpha$ proteins were later found to be the relevant G-protein components [30,46]. Heterotrimeric G-proteins were known to respond to extracellular signals, via seven-pass transmembrane receptors, so it was surprising to find a role for these proteins in the one-cell stage

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