

Small Regulatory RNAs May Sharpen Spatial Expression Patterns

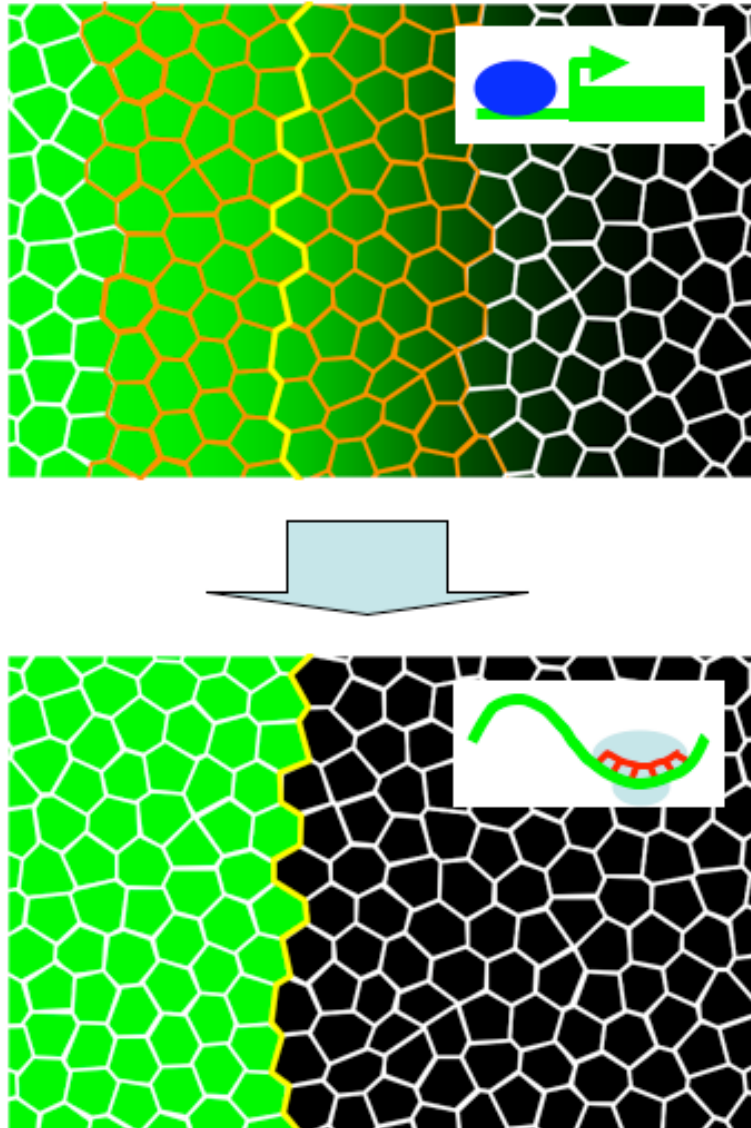
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The precise establishment of gene expression patterns is a crucial step in development. Formation of a sharp boundary between high and low spatial expression domains requires a genetic mechanism that exhibits sensitivity, yet is robust to fluctuations, a demand that may not be easily achieved by morphogens alone. Recently, it has been demonstrated that small RNAs (and, in particular, microRNAs) play many roles in embryonic development. While some RNAs are essential for embryogenesis, others are limited to fine-tuning a predetermined gene expression pattern. Here we explore the possibility that small RNAs participate in sharpening a gene expression profile that was crudely established by a morphogen. To this end we study a model where small RNAs interact with a target gene and diffusively move from cell to cell. Though diffusion generally smears spatial expression patterns, we find that intercellular mobility of small RNAs is actually critical in sharpening the interface between target expression domains in a robust manner. This sharpening occurs because small RNAs diffuse into regions of low mRNA expression and eliminate target molecules therein, but cannot affect regions of high mRNA levels. We discuss the applicability of our results, as examples, to the case of leaf polarity establishment in maize and Hox patterning in the early *Drosophila* embryo. Our findings point out the functional significance of some mechanistic properties, such as mobility of small RNAs and the irreversibility of their interactions. These properties are yet to be established directly for most classes of small RNAs. An indirect yet simple experimental test of the proposed mechanism is suggested in some detail.



Graphic depiction of a mature tissue containing two cell types distinguished by the fact that a given gene is expressed at high levels in one (green) and at low levels in the other (black). Top: Transcriptional regulation of this target gene, eg. via a shallow gradient of morphogen (shown in blue in the inset), may result in cells exhibiting intermediate expression levels of the gene at the tissue boundary between the two cell types (cells exhibiting intermediate levels are outlined in orange). Bottom: To ensure proper development, these ambiguous cells must be fine-tuned towards one or the other cell type. We used a computational approach to show how small regulatory RNAs (depicted in red in the inset) may accomplish this at the posttranscriptional level by interacting with the gene's mRNA (green in inset).