506c Cell Fate Determination by Multiple Signaling Pathways: Genome-Wide Analysis and Modeling of Pattern Formation in *Drosophila* Egg Development

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In development, intracellular signaling pathways act together to regulate spatiotemporal patterns of gene expression and guide tissue morphogenesis.[1] We use fruit fly egg development (oogenesis) as an experimental system to investigate how a combination of signaling pathways control gene expression in developing epithelial layers.[2] During oogenesis, two main pathways control pattern formation and eggshell morphology. The first pathway is controlled by the epidermal growth factor receptor (EGFR), and the second is controlled by the fly homolog to the mammalian bone morphogenetic protein (BMP) receptor. Gene expression induced by a combination of EGFR and BMP pathways establishes the dorsoventral polarity of the egg and of the future *Drosophila* embryo. While multiple genes have been found to require both pathways for their expression, the total number of the genes responding to both EGFR and BMP in oogenesis and their spatial patterns is still unknown.[3] As a first step to identifying the genes controlled by EGFR and BMP signaling, we conducted a genome wide screen using Affymetrix GeneChip microarrays and have validated the results of this screen in large-scale quantitative real-time PCR and *in situ* hybridization experiments. As an example, two genes, pipe and rhomboid, identified by these approaches were studied in detail using a combination of computational modeling and experiments. Pipe, an enzyme critical for transmission of the dorsoventral polarity from the egg to the embryo is repressed by EGFR activity and was found, in our screen, to be activated by BMP signaling.[4] We use simple reaction-diffusion modeling to interpret how EGFR and BMP pathways establish the spatial pattern of pipe expression. The second gene is rhomboid, an intracellular protease that is involved in a positive feedback loop in the EGFR network.[5] We have discovered that, at the level of a single cell, the expression of rhomboid exhibits a nonmonotonic dependence on the level of activation of both EGFR and BMP pathways. We use the experimentally observed spatial patterns of rhomboid expression in multiple genetic backgrounds to infer the quantitative input/output maps that convert the levels of EGFR and BMP signals into the level of rhomboid expression in oogenesis. The combination of genomics, genetic approaches, and computational modeling should reveal new expression patterns that will elucidate cell fate determination by multiple intracellular signaling pathways.

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