

Bicoid

Bicoid is the protein product of a maternal-effect gene unique to flies of the genus *Drosophila*. In 1988 Christiane Nüsslein-Volhard identified bicoid as the first known morphogen. A morphogen is a molecule that determines the fate and phenotype of a group of cells through a concentration gradient across that developing region. The bicoid gradient, which extends across the anterior-posterior axis of *Drosophila* embryos, organizes the head and thorax.

The discovery of the first morphogen not only bolstered the study of embryonic pattern formation, but it also vindicated a concept more than one hundred years old. In 1901 Thomas Hunt Morgan hypothesized that a sort of stuff acted at different concentration levels to organize regeneration in hydroids, planarians, and annelids. In 1952 Alan Turing defined Morgan's stuff as a morphogen. Turing's paper "The Chemical Basis of Morphogenesis," defined a morphogen as a molecule in the embryo that diffuses between cells and, at certain concentrations variably controls embryonic development. Eighteen years later, in 1970, Francis Crick authored "Diffusion in Embryogenesis," the first detailed model of how a chemical morphogen could establish a gradient over a small field of cells.

Despite the work of Crick and Turing, an actual morphogenic molecule had not been identified, hence the concept of morphogens was entirely theoretical. However, in 1978 when Nüsslein-Volhard began collaborating with Eric Wieschaus at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, they sought to investigate pattern formation in *Drosophila* and to analyze genes that were potential morphogens. Pattern formation occurs when homogenous embryonic cells receive genetic instructions, and form distinctive physiological segments, establishing the body plan of the embryo. Nüsslein-Volhard and Wieschaus systematically examined mutant fly embryos to elucidate the genetic mechanisms at work during the formation of the body plan. At the EMBL the two performed a series of genetic screens to detect mutations in *Drosophila* embryos that affected segmentation, which is the formation of distinct body segments during embryogenesis. On the basis of this work Nüsslein-Volhard and Wieschaus won the 1995 Nobel Prize in Physiology or Medicine, which they shared with fellow *Drosophila* geneticist Edward Lewis for his independent work in homeotic mutations.

The towering amount of data produced by the screens also made distinguishing the effects of different genes difficult. To simplify the process, Nüsslein-Volhard's lab began a second set of screens focusing on maternal effect genes in 1980. Maternal effect genes are genes whose products are inserted into the egg by the mother, and they control embryogenesis before activation of the genome of the embryo. These studies yielded still more genes with an effect on pattern development. Nüsslein-Volhard and Hans-Georg Frohnhofer, Nüsslein-Volhard's first graduate student, showed that the bicoid gene is key in patterning the anterior-posterior (A-P) axis. Frohnhofer demonstrated that of all the maternal effect of genes in *Drosophila*, only loss of bicoid caused a complete absence of the head and thorax in mutant embryos.

Frohnhofer also showed that the *Drosophila* with mutated bicoid genes, organisms that wouldn't normally develop heads or thoraxes, could be completely rescued by an injection of cytoplasm containing the bicoid protein. The efficacy of these cytoplasmic rescue experiments depended on where in the embryo the cytoplasm was injected. Bicoid protein injected into the anterior pole of embryos most effectively rescued a normal phenotype, with decreasing efficacy as the injections moved towards the posterior pole. This result indicated that the anterior pole of the embryo must be the source of bicoid protein, and as the molecule diffuses across the embryo different concentrations of bicoid controlled the development of head and thoracic regions. This evidence implied that bicoid

protein not only helped establish the A-P axis, but also that high concentrations of the bicoid protein helped develop flies' head and thoracic segments.

To investigate these implications, Nüsslein-Volhard's group showed that during the production of female gametes (oocytes), bicoid messenger RNA (mRNA) localizes in the anterior pole, and extends posteriorly to twenty percent of the embryo's length. Nüsslein-Volhard, with the help of graduate student Wolfgang Driever, then used anti-bicoid antibody staining to demonstrate that the bicoid protein, for which the mRNA codes, forms a gradient just after a fly lays her egg. The gradient is established in the anterior pole by the production of bicoid protein from bicoid mRNA, and extends greater than sixty percent of the embryo. As bicoid protein moves away from the anterior pole, the concentration of bicoid drops sharply. Furthermore, the gradient persists well after gastrulation and translates directly into the pattern of the embryo along the A-P axis.

Despite the evidence that bicoid was a morphogen based on the concentration gradient and the phenotypic abnormalities observed, Nüsslein-Volhard's group did not know the molecular mechanism by which bicoid controlled segmentation. However, it was known that the coding region of the bicoid gene contained a homeobox, a conserved 180 base pair sequence that is found in genes that control pattern formation in a wide range of organisms. Genes that contain the homeobox sequence are called Hox genes, and control body plan development by regulating the transcription of downstream genes. The presence of the homeobox indicated that bicoid influences the transcription of many genes, and that these genes are able to interpret various concentrations of the morphogen. However, the molecular mechanisms by which bicoid controlled these genes was not understood.

Nüsslein-Volhard and Driever published their findings in two papers in 1988. The product of the bicoid gene is widely accepted as the first discovered morphogen, and between 1988 and 2003 more than 700 papers were published on morphogens. However, there remains some controversy around the subject. When Nüsslein-Volhard and Driever published their findings, they did not propose a model for how embryonic cells interpret the bicoid gradient or how different concentrations produce different responses. Since then, scientists have proposed several models for how genes interpret and respond to varying concentrations of bicoid, however no one model has accounted for all of the bicoid gene's developmental effects.

Sources

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