**Bicoid** [1]

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The discovery of the first morphogen not only bolstered the study of embryonic pattern formation [8], but it also vindicated a concept more than one hundred years old. In 1901 Thomas Hunt Morgan [9] hypothesized that a sort of stuff acted at different concentration levels to organize regeneration in **hydroids** [10], planarians, and annelids. In 1952 Alan Turing defined Morgan’s stuff as a morphogen. Turing’s paper “The Chemical Basis of **Morphogenesis** [11],” 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 [12] 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 [13] was entirely theoretical. However, in 1978 when Nüsslein-Volhard began collaborating with Eric Wieschaus [14] at the **European Molecular Biology Laboratory** [15] (EMBL) in Heidelberg, Germany, they sought to investigate pattern formation [8] in *Drosophila* [4] embryos and to **analyze genes** [16] that were potential morphogens [13]. 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** [17] to detect mutations in *Drosophila* [4] embryos that affected segmentation [18], which is the formation of distinct body segments during embryogenesis [19]. On the basis of this work Nüsslein-Volhard and Wieschaus won the 1995 **Nobel Prize in Physiology or Medicine** [20], which they shared with fellow *Drosophila* [4] 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 [16] difficult. To simplify the process, Nüsslein-Volhard’s lab began a second set of screens focusing on maternal effect genes [16] in 1980. Maternal effect genes [16] are genes [16] whose products are inserted into the egg [21] by the mother, and they control embryogenesis [19] before activation of the genome [22] of the embryo. These studies yielded still more genes [16] with an effect on pattern development. Nüsslein-Volhard and Hans-Georg Frohnhöfer [23], Nüsslein-Volhard’s first graduate student, showed that the **bicoid** [6] gene is key in patterning the anterior-posterior (A-P) axis. Frohnhöfer demonstrated that of all the maternal effect of genes [16] in *Drosophila* [4], only loss of **bicoid** [6] caused a complete absence of the head and thorax in mutant embryos.

Frohnhöfer also showed that the *Drosophila* [4] with mutated **bicoid** [6] genes [16], organisms that wouldn't normally develop heads or thoraxes, could be completely rescued by an injection of cytoplasm containing the **bicoid** [6] protein. The efficacy of these cytoplasmic rescue [24] 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** [6] protein, and as the molecule diffuses across the embryo different concentrations of **bicoid** [6] controlled the development of head and thoracic regions. This evidence implied that **bicoid** [6] protein not only helped establish the A-P axis, but also that high concentrations of the **bicoid** [6] 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** [6] 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 [25], then used anti-**bicoid** [6] antibody staining to demonstrate that the **bicoid** [6] protein, for which the mRNA codes, forms a gradient just after a fly lays her egg [21]. The gradient is established in the anterior pole by the production of **bicoid** [6] protein from **bicoid** [6] mRNA, and extends greater than sixty percent of the embryo. As **bicoid** [6] protein moves away from the anterior pole, the concentration of **bicoid** [6] drops sharply. Furthermore, the gradient persists well after gastrulation [26] and translates directly into the pattern of the embryo along the A-P axis.

Despite the evidence that **bicoid** [6] 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** [6] controlled segmentation [18].
However, it was known that the coding region of the \textit{bicoid} \cite{6} gene contained a \textit{homeobox} \cite{27}, a conserved 180 base pair sequence that is found in \textit{genes} \cite{16} that control \textit{pattern formation} \cite{8} in a wide range of organisms. Genes that contain the \textit{homeobox} \cite{27} sequence are called \textit{Hox genes} \cite{28}, and control body plan development by regulating the transcription of downstream \textit{genes} \cite{16}. The presence of the \textit{homeobox} \cite{27} indicated that \textit{bicoid} \cite{6} influences the transcription of many \textit{genes} \cite{16}, and that these \textit{genes} \cite{16} are able to interpret various concentrations of the morphogen. However, the molecular mechanisms by which \textit{bicoid} \cite{6} controlled these \textit{genes} \cite{16} was not understood.

Nüsslein-Volhard and Driever published their findings in two papers in 1988. The product of the \textit{bicoid} \cite{6} gene is widely accepted as the first discovered morphogen, and between 1988 and 2003 more than 700 papers were published on \textit{morphogens} \cite{13}. 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 \textit{bicoid} \cite{6} gradient or how different concentrations produce different responses. Since then, scientists have proposed several models for how \textit{genes} \cite{16} interpret and respond to varying concentrations of \textit{bicoid} \cite{6}, however no one model has accounted for all of the \textit{bicoid} \cite{6} gene’s developmental effects.

\textbf{Sources}


\textbf{Associated Links}

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Bicoid is the protein product of a maternal-effect gene unique to flies of the genus \textit{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 \textit{Drosophila} embryos, organizes the head and thorax.