Bicoid [1]

By: Resnik, Jack Keywords: Morphogens [2]

Bicoid is the protein product of a maternal-effect gene [3] unique to flies of the genus *Drosophila* [4]. In 1988 Christiane Nüsslein-Volhard [5] identified bicoid [6] 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 [6] gradient, which extends across the anterior-posterior axis [7] of *Drosophila* [4] embryos, organizes the head and thorax.

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

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

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Subject

Nüsslein-Volhard, C. (Christiane) [34] Embryos [35] Morphogenesis [36] Turing, Alan Mathison, 1912-1954 [37] Morgan, Thomas Hunt, 1866-1945 [38] Crick, Francis, 1916-2004 [39] Wieschaus, Eric F. [40] Genes [41] Driever, Wolfgang [42] Homeobox genes [43] bicoid protein, Drosophila [44]

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Arizona State University. School of Life Sciences. Center for Biology and Society. Embryo Project Encyclopedia.

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Last Modified

Wednesday, July 4, 2018 - 04:40

DC Date Accessioned

Monday, August 13, 2012 - 21:48

DC Date Available

Monday, August 13, 2012 - 21:48

DC Date Created

2012-06-02

DC Date Created Standard

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