The Notch Signaling Pathway in Embryogenesis [1]

By: Wolter, Justin Keywords: Embryogenesis [2] Differentiation [3]

The Notch signaling pathway is a mechanism in animals by which adjacent cells communicate with each other, conveying spatial information and genetic instructions for the animal's development. All multicellular animals utilize Notch signaling, which contributes to the formation, growth, and development of embryos (embryogenesis [4]). Notch signaling also contributes to the differentiation [5] of embryonic cells into various types of cells, such as neurons. Research into the *Notch* gene in fruit flies began in the early twentieth century, but not until the end of the twentieth century did researchers begin to uncover, in many different species, the roles of Notch proteins for cell to cell signaling. Researchers have also found that dysfunction in the pathway can contribute to diseases such as cancer and Alzheimer's.

The Notch signaling pathway involves two adjacent cells, one that sends the signal, and one that receives and reacts to that signal. The Notch protein, called a receptor, extends from the receiving cell's cytoplasm, through that cell's outer membrane, and into the extracellular space. On the surface of the adjacent cell there is a protein, called a ligand, that connects to the Notch protein of the receiving cell. When the ligand of the signaling cell binds to the Notch receptor of the receiving cell, the portion of the Notch protein inside of the receiving cell changes its shape, and it is cleaved from the rest of the protein that is anchored in the membrane. The severed strand travels to the receiving cell's nucleus [6] and triggers a cascade of interactions between molecules that bind to DNA and that activate or repress the transcription of specific genes [7]. These interactions affect which proteins are produced in the receiving cell, and they ultimately direct its differentiation [5] into a more mature and functional cell.

In 1914, John S. Dexter worked at Olivet College in Olivet, Michigan, and he worked with fruit flies from the species *Drosophila melanogaster* [8]. Dexter noticed a heritable abnormality in some flies, which had small notches in the tips of their wings. Three years later Thomas Hunt Morgan [9], intrigued by the heritability of such changes, identified the first allele of the *Notch* gene while working at Columbia University [10], in New York City, New York. By the mid 1920's, Morgan and his students had identified multiple mutant *Notch* alleles, many of which were lethal, but some of which resulted in notched wings, or in abnormal hair bristles on female flies. However, as the number of identified alleles began to grow, so did the recorded number of phenotypic responses. Morgan observed that mutations to the *Notch* gene, conceptualized at the time as some unit of inheritance located on chromosomes, showed inconsistent behaviors, causing the gene to lose its function, to gain new functions, or to produce more protein. Such mutations also revealed both recessive and dominant patterns within populations of fruit flies. These mutational responses confounded researchers who tried to label the locus of the *Notch* gene with a specific developmental function.

Starting in the mid 1930s, Donald Poulson removed entire chromosomes from the cells in *Drosophila* [11] embryos and described the effects on the development of those embryos. Poulson first described his results in his 1936 doctoral dissertation for the Department of Embryology at the Carnegie Institute of Washington, in Baltimore, Maryland. Poulson worked to attribute aspects of specific genes [7] on these chromosomes, but he viewed removal of entire chromosomes as a blunt method for revealing less specific, far-reaching phenotypic changes. However, Poulson did characterize a few chromosomal deficiencies, where only a portion of the chromosome was mutated. One such abnormality included the *Notch* locus. Poulson wrote that fly embryos that lacked the *Notch* gene developed normally through the first four hours of embryogenesis [4], but then failed to develop two of the three germ layers [12]; the mesoderm and endoderm. Poulson's detailed description of *Notch* mutants was one of the first associations of the actions of a specific gene on morphogenesis in any organism.

Despite these findings, few elaborated on Poulson's work for nearly forty years. Some suggest that perhaps Poulson's work was overshadowed by the scientific celebrity of Morgan's lab, which focused on the genetics of the adult fly. Furthermore, Poulson attracted few graduate students, partly because of the technical constraints associated with work on fly embryos. Compared to other commonly used animal models at the time, such as sea urchins, chicks, and amphibians [13], *Drosophila* [11] eggs are small and difficult to manipulate. Additionally, scientists noted that most embryos with mutations to the *Notch* gene simply died. As biologist Scott Gilbert [14] said when he later described the lack of interest in Poulson's work, "Death is a difficult phenotype to analyze." In the decades following Poulson's work, many used *Drosophila* [11] in the larval and adult stages to study genetics and inheritance, but research on the early embryogenesis [4] stalled.

Work on *Drosophila* [11] embryogenesis [4] intensified in the 1970's in Walter Gehring's lab at the University of Basel [15] in Basel, Switzerland. Two of Gehring's post doctoral researchers, Eric Wieschaus [16], a graduate student of Poulson's, and Christiane Nüsslein-Volhard [17], continued to investigate fly embryogenesis [4] at the European Molecular Biology Laboratory [18] in Heidelberg, Germany. Weischaus and Nüsslein-Volhard identified and characterized many of the genes [7] and gene products that help establish the polarity [19] and segmentation [20] patterns in fly embryos, among them several *Hox* genes [7] and genes [7] involved in major signaling pathways, such as *hedgehog*. Researchers subsequently identified many homologs of these fly

genes [7] in vertebrates. Weischaus and Nüsslein-Volhard, along with fellow geneticist and discoverer of the homeobox [21] Edward Lewis, received the Nobel Prize in Physiology or Medicine[22] in 1995 for their work on *Drosophila* [11] embryogenesis [4].

In 1983 Spyros Artavanis-Tsakonas led an early molecular inquiry into the*Notch* gene locus in *Drosophila* [11] at Yale University [23] in New Haven, Connecticut. By cloning [24] fragments of *Notch* complimentary DNA (cDNA) and aligning overlapping sequences, Artavanis-Tsakonas described the nucleotide sequence of the *Notch* gene and the amino acid sequence of the Notch protein. By comparing the sequences to other known proteins, Spyros-Tsakonas hypothesized that the Notch protein spanned the cell membrane and contained a region that extended outside the cell. This region, called the epidermal growth factor repeat (EGF-repeat), is a cysteine-rich sequence of amino acids, and it exists in all animals. Artavanis-Tsakonas's research confirmed that EGF-repeats are the primary region where the Notch protein interacts with its ligand. The sequencing of the *Notch* gene revealed the function of the gene product for the first time, indicating that the Notch protein acts as part of a signaling cascade that communicates molecular signals between neighboring cells. Afterwards, researchers worked to characterize the Notch protein and the molecules that comprise the Notch signaling pathway.

Shortly after Artavanis-Tsakonas sequenced the *Notch* gene, various ligand proteins began to receive attention. The first ligand to be sequenced was Delta in 1987, followed by Serrate in 1990, and Lag-2 in 1994. The ligands were similar to the Notch receptor in that they span the cell membrane, extend into the space outside the cell, and contain EGF-repeat regions. Those results supported the theory that Notch signaling is a mechanism of communication between adjacent cells. Over the next several years researchers found that the Notch signaling pathway was active in many cellular processes in a variety of model organisms. In 1988 researchers showed that the Notch protein mediates cell signaling and differentiation [5] in anchor cells and vulval cells in the worm *Caenorhabditis elegans* [25], and in 1989 others showed similar roles for the Notch protein in eye development and in neurogenesis of *Drosophila* [11].

In 1991, evidence accumulated that Notch signaling participates in a wide range of developmental processes, Leif Ellisen, a cancer researcher at Brigham and Women's Hospital and Harvard Medical School [26] in Boston, Massachusetts, made the first connection between Notch signaling and human health. Ellisen discovered that an abnormal relocation of an uncharacterized gene occurred in a high percentage of lymphoblastic leukemia cells. Upon sequencing this gene, Ellisen showed that it was similar to the *Notch* gene in *Drosophila* [11], revealing the existence of Notch signaling inhumans [27]. Furthermore, his results indicated that deleting a member of the signaling pathway can contribute to the development of cancer. Ellisen's results sparked much research into the *Notch* gene and its relations to human health.

Since Ellisen's discovery, the Notch signaling pathway has been found in nearly all multicellular animals. All mammals have four different *Notch* genes [7] in their genomes and at least five ligands that bind to Notch proteins: three Delta-like ligands and two Jagged ligands (homologous to Serrate in *Drosophila* [11]), each of which differ in their number of EGF repeats. The different *Notch* genes [7] and proteins indicate that the Notch pathway has at least several roles in mammalian development. Notch signaling has been found to be active in many of the processes during embryogenesis [4], including the differentiation [5] of neurons (neurogenesis), somite formation (somitogenesis [28]), muscle tissue formation (myogenesis), heart formation (cardiogenesis), formation of the cellular components of the blood (haematopoeisis), and formation and maturation of blood vessels (vasculogenesis and angiogenesis [29], respectively), among others.

The Notch signaling pathway is composed of many proteins that are sequentially activated. The Notch signal is initiated when the Notch receptor protein comes into contact with its ligand located on an adjacent cell. When the receptor and ligand interact through the EGF-repeat region, the intracellular portion of the Notch protein (Notch intracellular domain [NICD]) is cleaved from the extracellular portion of the Notch protein. The NICD then moves into the cell nucleus [6]. Once in the nucleus [6] the NICD binds to a transcription factor that, in the absence of the NICD, normally represses target genes [7]. When the NICD binds to the transcription factor, they form a large protein complex that activates the expression of target genes [7]. The genes [7] activated differ depending on the cell type and on the developmental context.

While there are many nuances in Notch signaling in different cell types and in different stages ofembryogenesis [4], Notch signaling regulates cellular activities in several general ways. For example, Notch signaling can promote or repress cellular proliferation, maintain stem cell populations, specify cell fates, control differentiation [5], and mediate cell death (apoptosis [30]). Some proteins, called effector proteins, can also alter the intensity of Notch signaling based on the surrounding type of tissue or the developmental stage. Examples of these regulatory proteins in Notch signaling include Lunatic fringe, which can impact the affinity of Notch for its ligands; Numb, which helps to remove the Notch receptor from the cell membrane and to degrade it; and Mastermind, which impacts the ability of Notch to regulate gene transcription. Together with the many other regulatory elements of the Notch signaling pathway, these mechanisms balance the cellular interactions that occur throughout the developing organism.

As research relating to the role of Notch signaling inembryogenesis [4] continues, researchers investigate its role in disease. Notch signaling has been implicated in such diverse diseases as Alzheimer's disease, bone diseases, and heart defects. Since its identification in lymphoblastic leukemia, Notch signaling has also been identified in many types of cancer. The most apparent effects of changes in Notch regulation [31] are in promoting cancerous proliferation, and in inhibitingapoptosis [30]. As of early 2013, clinical trials are under way for therapies aimed at lymphoblastic leukemia, breast cancer, colon cancer, and glioblastoma, the most common and most aggressive malignant brain tumor in humans [27].

Sources

1. Baron, Martin, Hau Aslam, Marzena Flasza, Maggy Fostier, Jenny Higgs, Sabine L Mazaleyrat, and Marian B. Wilkin. "Multiple Levels of Notch Signal Regulation (Review)." *Molecular Membrane Biology* 19 (2002): 27–38.
2. Cormier, Sarah, Celine Souilhol, Charles Babinet, and Michel Cohen-Tannoudji. "Notch Signalling Pathway and Early Mammalian Embryogenesis." *Médecine Sciences* 23 (2007): 26–8.
3. Dexter, John S. "The Analysis of a Case of Continuous Variation in Drosophila [11] by a Study of Its Linkage Relations." *The American Naturalist* 48 (1914): 712–58.
4. D'Souza, Beryl, Laurence Meloty-Kapella, and Gerry Weinmaster. "Chapter Three - Canonical and Non-Canonical Notch Ligands." *Current Topics in Developmental Biology* [32] 86 (2010): 73–129.
5. D'Souza, Beryl, Alison Miyamoto, and Gerry Weinmaster. "The Many Facets of Notch Ligands."*Oncogene* 27 (2008): 5148–67.
6. Dumortier, Alexis, Anne Wilson, H. Robson MacDonald, and Freddy Radtke. 2005. "Paradigms of Notch Signaling in Mammals." *International Journal of Hematology* 82 (2005): 277–84.
7. Ellisen, Leif W., Jeffrey Bird, Daniel C. West, A. Lee Soreng, Thomas C. Reynolds, Stephen D. Smith, and Jeffrey Sklar. "TAN-1, The Human Homolog of the Drosophila [11] Notch Gene, is Broken by Chromosomal Translocations in T Lymphoblastic Neoplasms." *Cell* 66 (1991): 649–61.
8. Gazave, Eve, Pascal Lapebie, Gemma S. Richards, Frederic Brunet, Alexander V. Ereskovsky, Bernard M. Degnan, Carole Borchiellini, Michel Vervoort, and Emmanuelle Renard. "Origin and Evolution of the Notch Signalling Pathway: An Overview From Eukaryotic Genomes." *BMC Evolutionary Biology* 9 (2009): 249.
9. Gering, Martin, and Roger Patient. "Notch Signalling and Haematopoietic Stem Cell Formation During Embryogenesis." *Journal of Cellular Physiology* 222 (2010):11–6.
10. Gilbert, Scott F. *Developmental Biology* [32], 8th ed. Sundarland, MA: Sinauer, 2006.
11. Han, Jianxun, Micahel Hendzel, Joan Allalunis-Turner. "Notch Signaling as a Therapeutic Target for Breast Cancer Treatment?" *Breat Cancer Research* 13 (2011): 210–218.
12. Ilagan, Ma. Xenia and Raphael Kopan. "SnapShot: Notch Signaling Pathway." *Cell* 128 (2007): 1246.
13. Johansen, Kristen M., Richard G. Fehon, and Spyros Artavanis-Tsakonas. "The Notch Gene Product Is on the Cell Surface of Both Epidermal and Neuronal Precursor Cells during Drosophila [11] Development." *The Journal of Cell Biology* 109 (1989): 2427–2440.
14. Keller, Evelyn Fox. "Drosophila [11] Embryos as Transitional Objects: the Work of Donald Poulson and Christiane Nusslein-Volhard." *Historical Studies in the Physical and Biological Sciences* 26 (1996): 313–346.
15. Kidd, Simon, Mary K. Baylies, Gregory P. Gasic, and Michael W. Young. "Structure and distribution of the Notch protein in developing Drosophila [11]." *Genes & Development* 3 (1989): 1113–1129.
16. Kopan, Rafael, ed. *Notch Signaling.* San Diego: Academic Press, 2010.
17. Lendahl, Urban. "A Growing Family of Notch Ligands." *Bioessays* 20 (1998):103–7.
18. Morgan, Thomas H. "The Theory of the Gene." *The American Naturalist* 51 (1917): 513–44. http://dx.doi.org/10.5962/bhl.title.5978 [33] (Accessed January 11, 2013).
19. MacGrogan, Donal, Luis Luna-Zurita, and Jose Luis de la Pompa. "Notch Signaling in Cardiac Valve Development and Disease." *Birth Defects Research A: Clinical and Molecular Teratology* 91 (2011): 449–59.
20. Portin, Petter. "General Outlines of the Molecular Genetics of the Notch Signalling Pathway in Drosophila [11] Melanogaster: A Review." *Hereditas* 136 (2002): 89–96.
21. Poulson, Donald F. "Chromosomal Deficiencies and the Embryonic Development of *Drosophila* [11] *melanogaster*." *Proceedings of the National Academy of Sciences* [34] 23 (1937): 133–7.
22. Poulson, Donald F. and Metz, C. W. "Studies on the structure of nucleolus forming regions and related structures in the giant salivary gland chromosomes of Diptera." *Journal of Morphology* [35] 63 (1938): 363–95.
23. Theodosiou, Athina, Stilianos Arhondakis, Marc Baumann, and Sophia Kossida. "Evolutionary Scenarios of Notch Proteins." *Molecular Biology and Evolution* 26 (2009):1631–1640.
24. Wang, Zhiwei, Yiwei Li, Sanjeev Banerjee, and Fazlul H. Sarkar. "Exploitation of the Notch Signaling Pathway as a Novel Target for Cancer Therapy." *Anticancer Research* 28 (2008): 3621–30.
25. Wharton Kristin A., Kristen M Johansen, Tian Xu, Spyros Artavanis-Tsakonas "Nucleotide Sequence from the Neurogenic Locus Notch Implies a Gene Product that Shares Homology [36] With Proteins Containing EGF-Like Repeats." *Cell* 43 (1985): 567–81.
26. Woo, Ha-Na, Jong-Sung Park, A-Ryeong Gwon, Thiruma V. Arumugam, and Dong-Gyu Jo. 2009. "Alzheimer's Disease and Notch Signaling." *Biochemical and Biophysical Research Communications* 390 (2009): 1093–7.
27. Yochem, John, Kathleen Weston, and Iva Greenwald. "The Caenorhabditis elegans [37] lin-12 gene encodes a transmembrane protein with overall similarity to Drosophila [11] Notch." *Nature* 335 (1988): 547–550.

The Notch signaling pathway is a mechanism in animals by which adjacent cells communicate with each other, conveying spatial information and genetic instructions for the animal's development. All multicellular animals utilize Notch signaling, which contributes to the formation, growth, and development of embryos (embryogenesis). Notch signaling also contributes to the differentiation of embryonic cells into various types of cells into various types of cells, such as neurons. Research into the Notch gene in fruit flies began in the early twentieth century, but not until the end of the twentieth century did researchers begin to

uncover, in many different species, the roles of Notch proteins for cell to cell signaling. Researchers have also found that dysfunction in the pathway can contribute to diseases such as cancer and Alzheimer's.

Subject

Embryological development [38] Developmental biology [39] Embryos [40] Cell differentiation [41] Morgan, Thomas Hunt, 1866-1945 [42] Notch genes [43] Notch proteins [44] Nobel Prize winners [45] Drosophila melanogaster [46] Cell Communication [47] Signal Transduction [48] Receptors, Notch [49] Notch Proteins [50]

Topic

Processes [51]

Publisher

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

Rights

Format

Articles [52]

Last Modified

Wednesday, July 4, 2018 - 04:40

DC Date Accessioned

Monday, March 18, 2013 - 23:34

DC Date Available

Monday, March 18, 2013 - 23:34

DC Date Created

2013-03-06

DC Date Created Standard

Wednesday, March 6, 2013 - 07:00

- Contact Us

- The Embryo Project at Arizona State University, 1711 South Rural Road, Tempe Arizona 85287, United States

---

Source URL: https://embryo.asu.edu/pages/notch-signaling-pathway-embryogenesis

Links
[1] https://embryo.asu.edu/pages/notch-signaling-pathway-embryogenesis
[2] https://embryo.asu.edu/keywords/embryogenesis
[3] https://embryo.asu.edu/keywords/differentiation
[4] https://embryo.asu.edu/search?text=embryogenesis
[5] https://embryo.asu.edu/search?text=differentiation
[6] https://embryo.asu.edu/search?text=nucleus
[7] https://embryo.asu.edu/search?text=genes
[8] http://eol.org/pages/462/overview
[9] https://embryo.asu.edu/search?text=Thomas%20Hunt%20Morgan
[10] https://embryo.asu.edu/search?text=Columbia%20University
[11] https://embryo.asu.edu/search?text=Drosophila
[12] https://embryo.asu.edu/search?text=germ%20layers
[13] https://embryo.asu.edu/search?text=amphibians
[14] https://embryo.asu.edu/search?text=Scott%20Gilbert
[15] https://embryo.asu.edu/search?text=University%20of%20Basel
[16] https://embryo.asu.edu/search?text=Eric%20Wieschaus
[17] https://embryo.asu.edu/search?text=Christiane%20N%C3%BCsslein-Volhard

[18] https://embryo.asu.edu/search?text=European%20Molecular%20Biology%20Laboratory
[19] https://embryo.asu.edu/search?text=polarity
[20] https://embryo.asu.edu/search?text=segmentation
[21] https://embryo.asu.edu/search?text=homeobox
[22] https://embryo.asu.edu/search?text=Nobel%20Prize%20in%20Physiology%20or%20Medicine
[23] https://embryo.asu.edu/search?text=Yale%20University
[24] https://embryo.asu.edu/search?text=cloning
[25] http://eol.org/pages/403869/overview
[26] https://embryo.asu.edu/search?text=Harvard%20Medical%20School
[27] https://embryo.asu.edu/search?text=humans
[28] https://embryo.asu.edu/search?text=somitogenesis
[29] https://embryo.asu.edu/search?text=angiogenesis
[30] https://embryo.asu.edu/search?text=apoptosis
[31] https://embryo.asu.edu/search?text=regulation
[32] https://embryo.asu.edu/search?text=Developmental%20Biology
[33] http://dx.doi.org/10.5962/bhl.title.5978
[34] https://embryo.asu.edu/search?text=National%20Academy%20of%20Sciences
[35] https://embryo.asu.edu/search?text=Journal%20of%20Morphology
[36] https://embryo.asu.edu/search?text=Homology
[37] https://embryo.asu.edu/search?text=Caenorhabditis%20elegans
[38] https://embryo.asu.edu/library-congress-subject-headings/embryological-development
[39] https://embryo.asu.edu/library-congress-subject-headings/developmental-biology
[40] https://embryo.asu.edu/library-congress-subject-headings/embryos
[41] https://embryo.asu.edu/library-congress-subject-headings/cell-differentiation
[42] https://embryo.asu.edu/library-congress-subject-headings/morgan-thomas-hunt-1866-1945
[43] https://embryo.asu.edu/library-congress-subject-headings/notch-genes
[44] https://embryo.asu.edu/library-congress-subject-headings/notch-proteins
[45] https://embryo.asu.edu/library-congress-subject-headings/nobel-prize-winners
[46] https://embryo.asu.edu/library-congress-subject-headings/drosophila-melanogaster
[47] https://embryo.asu.edu/medical-subject-headings/cell-communication
[48] https://embryo.asu.edu/medical-subject-headings/signal-transduction
[49] https://embryo.asu.edu/medical-subject-headings/receptors-notch
[50] https://embryo.asu.edu/medical-subject-headings/notch-proteins
[51] https://embryo.asu.edu/topics/processes
[52] https://embryo.asu.edu/formats/articles