The Role of the Notch signaling pathway in Somitogenesis [1]

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Among other functions, the Notch signaling pathway contributes to the development of somites [4] in animals. It involves a cell signaling mechanism with a wide range of functions, including cellular differentiation [5], and the formation of the embryonic structures (embryogenesis [6]). All multicellular animals use Notch signaling, which is involved in the development, maintenance, and regeneration of a range of tissues. The Notch signaling pathways spans two cells, and consists of receptor proteins, which cross one cell´s membrane and interacts with proteins on adjacent cells, called ligands. The physical interaction of receptors and ligands directs the genetic response of the first cell to produce proteins that define the type of cell it will become. One of the earliest discovered roles of the Notch signaling pathway in vertebrates is in somite formation (somitogenesis [7]). Somitogenesis is the formation of somites [4], which are sphere-like structures in early vertebrate embryos that are the first visible signs of segmentation [8]. Somites then help to define many tissues and features of the adult animal´s body. The Notch signaling pathway plays at least two distinct roles during somitogenesis [7]: the first is maintenance of an oscillating protein gradient, called the segmental clock, and the second is establishing the polarity [9] of somites [4]. Mutations to genes [10] in the Notch pathway can result in birth defects [11] characterized by abnormal development of bones of the spine and ribs, like spondylocostal dysostosis. Additionally, dysfunction in the pathway linked to cancer progression, HIV-related complications, and Alzheimer´s disease, among other disorders.

Somites form early in embryogenesis [6] from embryonic tissue called the presomitic mesoderm [12] (PSM), and are the cellular precursors for skeletal muscle, dermis, and vertebrae tissues. Somitogenesis begins twenty-five days post fertilization [13] in humans [14] along the dorsal side of the developing embryo. Prior to somitogenesis [7], the PSM is a physically homogenous tissue, with no distinct spatial organization [15]. During somitogenesis [7], the somites [4] form from the PSM sequentially in a head to tail (anterior to posterior) direction. Nascent somites [4] are round structures, which form in bilateral pairs on either side of the neural tube [16]. During somitogenesis [7] proteins in the Notch signaling pathway provide a mechanism for adjacent cells to interact, coordinating the formation of somites [4] between cells along the length of the embryo, and regulating the expression of genes [10] that control the formation and subsequent differentiation [5] of somites [4] into mature tissues types.

John S. Dexter made the first observation of the role of the Notch signaling pathway in development while working at Olivet College in Olivet, Michigan, in 1914. Dexter, working with the fruit fly *Drosophila melanogaster* [17], observed a notch-like indentation in the wings of mutant flies. In 1917, Thomas Hunt Morgan [18], while working at Columbia University [19] in New York City, New York, identified a genetic locus that contributes to various notched mutant phenotypes. Using heritable traits such as the *Notch* locus, Morgan confirmed the chromosomal theory of inheritance, work for which he received the Nobel Prize in Physiology or Medicine [20] in 1933. Throughout the next several decades, researchers such as Richard Poulson at the Carnegie Institute of Washington, in Baltimore, Maryland, described the range

of phenotypic abnormalities associated with mutations in the *Notch* locus. Many researchers relied on the *Notch* gene to study how mutations to genes [10] affected phenotypes in adult organisms. They began to study more genes [10] when they started to sequence DNA sequencing in the early 1970s.

In 1983 Spyros Artavanis-Tsakonas and his research group at Yale University [21] in New Haven, Connecticut, sequenced the *Notch* gene in *Drosophila* [22] and discovered the Notch protein was likely a molecule bound to cell membranes. In 1991, Leif Ellisen, a cancer researcher at Brigham and Women´s Hospital and Harvard Medical School [23] in Boston, Massachusetts, discovered that in humans [14] with lymphoblastic leukemia, something disrupts the human *Notch* gene so that it doesn't produce its protein normally. The connection between a gene in *Drosophila* [22] development and in human cancer led to research on the *Notch* gene in vertebrates. In 1995 Ronald Conlon, working in the lab of Janet Rossant at the Samuel Lunenfeld Research Institute in Toronto, Ontario, discovered that the mice for which scientists had obstructed the production of the Notch protein during embryogenesis [6] develop a disorganized body plan. Conlon and his colleagues demonstrated that the *Notch* gene was expressed in the PSM and directly contributed to somitogenesis [7].

The Notch signaling pathway in mammals consists of four Notch proteins and a myriad of other proteins. The Notch receptor proteins of a cell interact with the Notch ligands of adjacent cells, a process that initiates the activity of the other proteins in the pathway. The Notch proteins span the cell membrane with a large extracellular domain (ECD) outside of the cell and a small intracellular domain (ICD). The Notch protein activates only after physical contact between the Notch receptor protein of one cell, and one of its ligands embedded in the membrane of an adjacent cell. Because the Notch protein and its ligand proteins are both membrane bound proteins, two cells must be close to each other for the pathway to activate. Once the ligand binds to the Notch receptor protein, proteins cleave the Notch protein´s ICD, and they shuttle it to the nucleus [24] of the cell. The ICD then interacts with various transcription factors and accessory proteins, which form a complex that regulates the expression of target genes [10]. The pathway is a mechanism by which cells can communicate their positions to each other, and by which they can drive the expression of genes [10] that will direct the fate of cells in the proper position in the embryo.

The Notch signaling pathway plays a role in at least two key aspects of somitogenesis [7]: the oscillating pattern of gene expression known as the segmental clock, and the establishment of anterior-posterior polarity [9] of somites [4]. Somites develop sequentially beginning in the anterior of the embryo and progress towards the extending tail bud. Some genes [10] that help form the boundaries between developing somites [4] also control the development of the somites [4] themselves. These genes [10] turn on and off in a wave-like pattern, with each wave corresponding to the formation of a new somite. The timing of these oscillations is critical for proper somite formation and segmentation [8] of the embryo, and is called the segmental clock. An example of a segmental clock in mice embryos can be seen in this video [25] (Supporting Movie 1), in which the oscillations represent the expression of the mouse [26] gene *Hes7*, a transcription factor that is part of the Notch signaling pathway. Each wave corresponds to the development of one pair of somites [4] in the mouse [26] (*Mus musculus* [27]) embryo, and somite boundaries can be seen forming caudally on the embryo (right of image, top). Two other developmental signaling pathways, Wnt and FGF, also exhibit oscillations in gene expression in somites [4], and help regulate somitogenesis [7] and the segmental clock.

At least two molecules interact in a negative feedback circuit that controls the oscillations of

gene expression. The first molecule is a receptor of Notch proteins, and the second is a cytoplasmic protein called Lunatic Fringe (Lfng), which is a expressed via the activated Notch signal. The activated Notch signal drives the transcription of the *Lfng* gene, which in turn produces a protein that reduces the affinity of the Notch receptors for their ligands, dampening the activation of the pathway. As Lfng proteins degrade shortly after binding to their target genes [10] on the DNA, they inhibit Notch proteins for a finite period, after which Notch receptors can reactivate and resume signal transduction. This is one mechanism by which the Notch signal moves through cells in a synchronized, rhythmic pattern, turning gene expression on and off. Because the Notch signal originates in the extending tail bud of an embryo, is transduced via adjacent cells, and contains a transient negative feedback mechanism, the signal oscillates anteriorly to where nascent somites [4] arise. Mice that have Notch genes [10] experimentally silenced or knocked out still develop somites [4], but the boundaries are chaotic and somite size varies from normal embryos significantly. Furthermore, mutations in genes [10] such as *Lfng* and *Hes7* involved in the Notch pathway can cause congenital spinal birth defects [11] such as spondylocostal dysostosis.

The second role of Notch signaling is to establish anterior-posterior polarity [9] of somites [4] through interactions with proteins that belong to the fibroblast growth factor (FGF) signaling pathway. In contrast to Notch, FGF proteins secreted from cells form a concentration gradient along the embryo with the highest levels in the extending tail bud. The Notch signal starts in the tail bud and moves through the presomitic mesoderm [12] until it reaches a region where there is little FGF protein. At this position in the embryo, the Notch signal ceases to oscillate, which causes some cells to form a somite. The position where the Notch signal terminates marks the front, or anterior half of the new somite, and initiates the expression of genes [10] that form the boundary between somites [4]. When the anterior boundary of the somite forms, different genes [10] begin to make their products that will define the anterior or posterior halves of the somite. Thus, not only do somites [4] distinguish themselves from neighboring somites [4] in what tissues they are the precursors of, but the poles within individual somites [4] also form distinct tissues.

The mechanism by which Notch and FGF initiate somitogenesis [7], define somite polarity [9], and direct cell fate is called the differentiation [5] wavefront model. Mice that have *Notch* genes [10] knocked out exhibit somites [4] with reversed polarity [9], resulting in tissues derived from somites [4] being upside-down in regards to their normal position in the embryo. Researchers argue that such reversals are caused by the disorientation of genes [10] such as *Mesp2* that are normally expressed in conjunction with *Notch* in the anterior portion of somites [4] at the front of the FGF signal.

Researchers work to describe the functions of Notch signaling. Based on evidence from chick [28] embryos, one proposed function of the pathway was that it helped furrow the PSM and form the border between somites [4]. However, in the late 2000s, researchers observed the presence of somite boundaries in both zebrafish and in mice for which the researchers had knocked out the *Nothch* genes [10], a result that challenged hypothesis of Notch signaling as the sole cause of somite border formation. Furthermore, researchers showed that the Notch signaling pathway operates exclusively from FGF and Wnt signaling pathways throughout somitogenesis [7], a result that confounded models that described Notch signaling as driving the segmentation [8] clock and the differentiation [5] wavefront through interactions with FGF and Wnt signaling pathways.

Sources

1. Christ, Bodo, Ruijin Huang, and Martin Scaal. "Amniote Somite Derivatives." *Developmental Dynamics* 236 (2007): 2382?96.
2. Cinquin, Oliver. "Understanding the Somitogenesis Clock: What's Missing?" *Mechanisms of Development* 124 (2007): 501?17.
3. Conlon, Ronald A., Andrew G. Reaume, and Janet Rossant [29]. "Notch1 is required for the coordinate segmentation [8] of somites [4]." *Development* 121 (1995): 1533?45. http://dev.biologists.org/content/121/5/1533.short [30] (Accessed March 22, 2014).
4. Dexter, John S. "The analysis of a case of continuous variation in Drosophila [22] by a study of its linkage relations." *American Naturalist* (1914): 712?58. http://www.biodiversitylibrary.org/item/140651#page/736/mode/1up [31] (Accessed March 22, 2014).
5. 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 [22] Notch Gene, is Broken by Chromosomal Translocations in T Lymphoblastic Neoplasms." *Cell* 66 (1991): 649?61.
6. Feller, Juliane, Andre Schneider, Karin Schuster-Gossler, and Achim Gossler. "Noncyclic Notch Activity in the Presomitic Mesoderm Demonstrates Uncoupling of Somite Compartmentalization and Boundary Formation." *Genes and Development* 22 (2008): 2166?71. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2518812/?report=classic [32] (Accessed March 22, 2014).
7. Ferjentsik, Zoltan, Shinichi Hayashi, J. Kim Dale, Yasumasa Bessho, An Herreman, Bart De Strooper, Gonzalo del Monte, Jose Luis de la Pompa, Miguel Maroto. "Notch Is a Critical Component of the Mouse Somitogenesis Oscillator and Is Essential for the Formation of the Somites." *PLOS Genetics* (2009): 1?14. http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1000662 [33] (Accessed March 22, 2014).
8. Gilbert, Scott F. *Developmental Biology* [34]. 8th ed. Sunderland, MA: Sinauer, 2010.
9. Mirandola, Leonardo, Sara Larocca, Katia Rea, Giovanni Palma, Paola Comi, and Raffaella Chiaramonte. "Notch: From Fly Wings to Human Hematological Tumors." *Archive of Oncology* 17 (2009): 72?7. http://www.onk.ns.ac.rs/archive/Vol17/V17n34p72.htm [35] (Accessed March 22, 2014).
10. Morgan, Thomas H. "The Theory of the Gene." *The American Naturalist* 51 (1917): 513?44. http://www.biodiversitylibrary.org/item/138632#page/513/mode/1up [36]
11. Niwa, Yasutaka, Hiromi Shimojo, Akihiro Isomura, Aitor Gonzalez, Hitoshi Miyachi, and Ryoichiro Kageyama. "Different Types of Oscillations in Notch and Fgf Signaling Regulate the Spatiotemporal Periodicity of Somitogenesis." *Genes and Development* 25 (2011): 1115?20. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3110950/?report=classic [37] (Accessed March 22, 2014).
12. Pourquie, Oliver. "Vertebrate Somitogenesis." *The Annual Review of Cell Developmental Biology* [34] 17 (2001): 311?50.
13. Sewell, William, Duncan Sparrow, Allanceson Smith, Dorian Gonzalez, Eric Rappaport, Sally Dunwoodie, and Kenro Kusumi. "Cyclical Expression of the Notch/Wnt Regulator Nrarp Requires Modulation by Dll3 in Somitogenesis." *Developmental Biology* [34] 329 (2009): 400?9. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2697309/?report=classic [38] (Accessed March 22, 2014).
14. Weinmaster, Gerry, and Chris Kintner. "Modulation of Notch Signaling During

Somitogenesis." *The Annual Review of Cell Developmental Biology* [34] 19 (2003): 367?95.
15. 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 [39] With Proteins Containing EGF-Like Repeats." *Cell* 43 (1985): 567?81.

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Subject

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[30] http://dev.biologists.org/content/121/5/1533.short
[31] http://www.biodiversitylibrary.org/item/140651#page/736/mode/1up
[32] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2518812/?report=classic
[33] http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1000662
[34] https://embryo.asu.edu/search?text=Developmental%20Biology
[35] http://www.onk.ns.ac.rs/archive/Vol17/V17n34p72.htm
[36] http://www.biodiversitylibrary.org/item/138632#page/513/mode/1up
[37] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3110950/?report=classic
[38] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2697309/?report=classic
[39] https://embryo.asu.edu/search?text=Homology
[40] https://embryo.asu.edu/library-congress-subject-headings/notch-genes
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