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Notching up another pathway

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Summary

The Notch proteins play a vital role in cell fate decisions in both invertebrate and vertebrate development. Careful analysis of this role has led to a model of signalling downstream of these receptors, via the CSL (CBF1, Suppressor of Hairless, Lag-1) family of transcription factors. However there have been suggestions that Notch can signal through other pathways. In the current paper, Ramain et al. (1) provide compelling evidence for Notch signalling through a CSL-independent pathway and they demonstrate that the cytoplasmic protein, Deltex, is required for this signal. In addition they show that Wnt signalling may regulate this Deltex dependent signal.

Keywords

Notch; Deltex; Wnt; cell signalling; cross-talk

Introduction

Notch genes encode large transmembrane proteins that act as receptors for the DSL (Delta, Serrate and Lag-2) family of ligands (2). These receptors are highly conserved, and play a crucial role in cell fate decisions during the development of organisms as diverse as sea urchins and humans (3). In addition, aberrant Notch signalling has been linked to several human diseases including a number of cancers, Alagille's syndrome and the neural degenerative disease, CADASIL, (4).

The best understood role of the Notch receptors in cell fate decisions is in the process of “lateral inhibition” which was first described during peripheral nervous system development in Drosophila (see figure 1) (5). The Drosophila thorax carries two types of sensory bristles, macrochaetae and microchaetae. Bristle development is initiated by prepattern genes and signalling through the Wingless pathway, which leads to the expression of proneural genes of the *achaete-scute complex* in small groups of cells (6-8). All the cells within these proneural clusters have the potential to develop into sense organ precursors (SOPs). However only one or two cells maintain *achaete-scute* expression and differentiate into SOPs, and in doing so emit an inhibitory signal that extinguishes proneural gene expression in their neighbours. This process is known as lateral inhibition. The selected SOPs will divide three times to produce the five cells of the sensory bristles including the external socket and bristle cells, and innervating neurone (9).

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Careful analysis of this lateral inhibition signal, together with experiments in other systems, has provided a detailed model for canonical DSL signalling (2) and a sensitive assay for Notch function. The signal is initiated by the interaction of the DSL ligands on the differentiating SOPs with the extracellular domain of the Notch proteins on neighbouring cells (see figure 1). This leads to two sequential proteolytic cleavages of the Notch protein, releasing the intracellular domain. This fragment of Notch enters the nucleus where it interacts with members of the CSL (CBF1, Suppressor of Hairless, Lag-1) family of transcription factors, converting the CSL proteins from transcriptional repressors into activators. During bristle development in Drosophila the association of the Notch intracellular domain with the Drosophila CSL protein, Suppressor of Hairless (Su(H)), leads to the expression of the bHLH transcription factors of the *Enhancer of split Complex (E(spl)-C)* (10). In turn the E(spl) proteins associate with the transcriptional co-repressor, Groucho (Gro), to inhibit *achaete-scute* expression.

Identification of a new class of Notch alleles

In the current paper, Ramain et al. (1) have isolated six new alleles (N^{Mcd1}, N^{Mcd2}, N^{Mcd5}, N^{Mcd7}, N^{Mcd8} and N^{Mcd9}) and identified one existing allele (N^{Mcd3}) of Notch in a genetic screen for mutations that specifically reduce the number of thoracic microchatae (see figure 1). These alleles appear to affect a Notch function as the N^{Mcd} phenotype changes when the copy number of the wild type *Notch* allele is altered. Furthermore, as Notch signalling inhibits bristle formation during normal development (11), the phenotype of the N^{Mcd} alleles suggests that they are gain of function mutations.

The phenotype of the N^{Mcd} alleles is reminiscent of two other classes of *Notch* alleles, the $l(1)N^{B}$-like and *Abruptex* (N^{Ax}) alleles (12). Like N^{Mcd} mutants, the number of microchaetae are reduced in flies of both these classes. The $l(1)N^{B}$-like class are easily distinguishable from the N^{Mcd} alleles genetically as the phenotype of the $l(1)N^{B}$-like mutants behaves differently when the copy number of the wild type *Notch* allele is altered (12). In contrast, the N^{Ax} alleles exhibit similar genetic behaviour to the N^{Mcd} alleles when wild type Notch function is increased or decreased (12). However N^{Ax} and N^{Mcd} alleles are distinguishable phenotypically. In the N^{Ax} mutants, macrochaetae are lost as well as microchaetae and they have broader wings, with shortened veins, than wild type flies. These phenotypes are not observed in $N^{Mcd}/+$ animals and suggest that increased canonical DSL signalling is occurring in $N^{Ax}/+$ flies.

Notch gain of function is independent of Lateral Inhibition

If the loss of microchaetae observed in the N^{Mcd} mutants is caused by increased signalling during lateral inhibition (see figure 1), the phenotype should be rescued when lateral inhibition is abolished. To test this possibility the authors have generated clones of N^{Mcd} cells that lack components required for lateral inhibition signalling (5). In all cases microchaetae fail to develop, indicating that the N^{Mcd} phenotype is not due to excessive signalling during lateral inhibition (see figure 1). Furthermore, as N^{Mcd} clones that lack Delta and Serrate function (the two known Drosophila DSL ligands) are indistinguishable from N^{Mcd} clones, the N^{Mcd} phenotype must be due to signalling of an unknown Notch ligand or an intrinsic activity of the Notch protein. Together these data indicate that the N^{Mcd} phenotype is due to increased signalling through a distinct intracellular pathway.

Proneural clusters are not defined in N^{Mcd} mutants

To analyse further the cause of N^{Mcd} phenotype the authors examined the expression of several marker genes that allow microchaetae differentiation to be monitored. Using the neural-specific antibody 22C10 (13), they demonstrated that the neurones that innervate the

sensory bristles are absent. Next they showed that SOPs fail to differentiate as expression of the SOP marker gene, *neuralised*, is absent (14). Further, they found that the proneural gene Achaete is not expressed in the N^{Mcd} mutants, indicating that the proneural clusters are not defined in the first place (6). Consequently it appears that the aberrant Notch signalling in the N^{Mcd} mutants is preventing the establishment of the proneural clusters.

A similar failure to establish normal proneural clusters is observed in the N^{Ax} mutants, (15) but in these flies the clusters are reduced in size rather than absent. This difference can explain the different phenotypes observed in clones of N^{Mcd} and N^{Ax} alleles where lateral inhibition signalling is abolished (see figure 1) (1, 16). In the N^{Ax} clones, multiple SOPs arise from the small proneural clusters when lateral inhibition is abolished leading to a tuft of bristles on the thorax. In contrast, in the N^{Mcd} animals no SOPs can develop even in the absence of lateral inhibition as the proneural clusters are absent.

The N^{Mcd} phenotype requires both Deltex and Shaggy

Deltex was originally implicated in Notch signalling because the phenotypes when the gene is mutated (17) or when the protein is over expressed (1, 18) mimic the phenotypes observed when Notch signalling is disrupted or activated respectively. In addition the Deltex protein has been shown to interact with the Notch intracellular domain suggesting that it functions downstream of the receptor (19). Ramain et al. (1) have shown that regularly spaced microchaetae develop in N^{Mcd},*deltex* double mutant clones, indicating that Deltex function is required for the N^{Mcd} phenotype. As the bristles are regularly spaced lateral inhibition signalling must be occurring normally. The authors have confirmed this by demonstrating that the N^{Mcd} proteins are cleaved to release the intracellular fragment which is indicative of DSL signalling (20, 21). Interestingly, *deltex* was originally isolated in a genetic screen for suppressers of a lethal combination N^{Ax} alleles (17) suggesting that the N^{Ax} phenotype is partly dependent upon signalling via Deltex as well.

Shaggy (Drosophila GSK-3β) is a central component of the Wingless signalling pathway which negatively regulates signalling through the pathway (22). However *shaggy* has also been shown to be epistatically downstream of Notch as *shaggy* mutations will rescue the N^{Ax} phenotype (23). Although this suggests that Shaggy may also be a component of a signalling pathway downstream of Notch, this result has generally been interpreted in the light of the fact that Notch and Wingless signalling have opposing effects on bristle development (see figure 1) (7, 11). Wingless signalling is required for the expression of the proneural gene, *achaete*. Therefore it has been suggested that unregulated Wingless signalling in the absence of Shaggy function will lead to Achaete expression and bristle development even when excessive Notch signalling is occurring (15, 24). It also appears that an unregulated Wingless signal can rescue the N^{Mcd} phenotype as microchaetae develop in double mutant clones for N^{Mcd} and *shaggy*.

Regulation of signalling by the N^{Mcd} proteins

The authors have characterised all seven alleles and found that all of them contain a mutation that will prematurely terminate the Notch protein C-terminal to the cdc10/ankyrin repeats, with the exception of N^{Mcd5} which is a mutation within EGF-like repeat 18 (see figure 2). In addition they noted that the severity of the phenotype is correlated with extent of the deletion. This region of Notch has previously been shown to interact with the Dishevelled protein, another intracellular component of the Wingless signalling pathway (25). The authors have confirmed in a two-hybrid analysis that the C-terminally deleted N^{Mcd} proteins are unable to interact with Dishevelled.

The rescue of the N^{Mcd} phenotype by removing Shaggy function suggests that a Wingless signal can inhibit the Notch signal that is activated by the N^{Mcd} mutations. Also Wingless signalling may inhibit Notch signalling via Deltex during normal development, as Wingless signalling is required for Achaete expression. Data from the careful analysis of two Wingless target genes support this possibility (26, 27). The expression of *S59* and *Ultrabithorax* in the somatic and visceral mesoderm respectively is dependent upon Wingless signalling, and expression of the two genes is lost or reduced in *wingless* mutant embryos (28, 29). However both genes are robustly expressed in the absence of a Wingless signal if Notch function is also removed (26, 27). In contrast removal of Su(H) function in a *wingless* mutant does not rescue the expression of either gene. This suggests that the expression of both genes is inhibited by Notch prior to the receipt of a Wingless signal and that a pathway that is distinct from the canonical Notch pathway is mediating the repression. It also suggests that the first step in Wingless signalling is to break this repression.

One way for a Wingless signal to regulate Notch signalling is through the interaction between Notch and Dishevelled (25). As the region of Notch required for this interaction is deleted in the N^{Mcd} proteins, this regulation would be abolished leading to unregulated Notch signalling via Deltex. The authors tested this possibility by over expressing Dishevelled in wild type and N^{Mcd} flies. In wild type flies, they found a mild but significant increase in the number of microchaetae, whereas microchaetae numbers are unaltered in the N^{Mcd} flies. This suggests that Dishevelled is able to regulate Notch signalling via Deltex through its interaction with the C-terminus of the Notch protein.

On the other hand, the clustering of the N^{Mcd5} and N^{Ax} mutations to a defined group of EGF-like repeats suggest that Notch signalling activated by the N^{Mcd} mutations could also be regulated by an extracellular ligand. For example the N^{Mcd5} and N^{Ax} mutations may be increasing the affinity of Notch for an unknown ligand that activates signalling via Deltex. On the other hand the mutations could be preventing the interaction of Notch with a ligand that inhibits Deltex dependent signalling. One interesting candidate for the inhibitory ligand is Wingless which has been shown by biopanning, immunoprecipitation and co-localisation studies to interact with the EGF-like repeats of Notch that are mutated in the N^{Mcd5} and N^{Ax} alleles (30).

Conclusions

Altogether these results, along with published data, suggest the following model for the development of the thorax microchaetae (see figure 3). The definition of the proneural clusters is initiated in the pupal wing disc by prepattern genes such as *pannier*, *ushaped*, *Bar* and elements of the *Iroquois complex* (6, 8). However Notch signalling via Deltex initially inhibits expression of the proneural genes in these clusters. Wingless signalling alleviates this repression through either the interaction of Dishevelled, Wingless or both with the Notch protein. This regulation of Notch signalling along with signalling through the canonical Wingless signalling pathway (7) leads to Achaete/Scute expression. Then lateral inhibition signalling via the canonical DSL pathway restricts Achaete/Scute expression to the one or two cells that will differentiate into SOPs (11). In this model, N^{Mcd} mutations disrupt the regulation Notch signalling via Deltex by Wingless or Dishevelled. Consequently the initial repression of Achaete/Scute expression is not broken and the proneural clusters fail to develop. In contrast, the reduced cluster size in the N^{Ax} mutants suggest that the ability of Wingless signalling to regulate Notch signalling via Deltex is reduced rather than abolished. Regulation of Notch signalling via Deltex by Wingless signalling could also explain the differences in phenotypes sometimes observed when Wingless signalling is activated by expressing Wingless and an activated Armadillo protein (see figure 3) (31, 32).

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Notch signalling via Deltex may have a more general role in repressing the expression of Wingless target genes. As described above Notch is required to repress *S59* and *Ultrabithorax* expression in the somatic and visceral mesoderm respectively prior to a Wingless signal (26, 27). Also ectopic and premature *engrailed* expression is observed in *Notch* mutant embryos (K. Brennan and A. Martinez Arias unpublished results).

Further evidence for Notch signalling via other intracellular pathways has come from experiments using the murine myoblast cell line C2C12 (33, 34). In these experiments the differentiation of C2C12 cells into myotubes is prevented by ectopically expressing a form of the Notch intracellular domain that cannot interact with CBF1, the mammalian CSL family protein. This suggests that activating a CBF1-independent pathway inhibits differentiation. The differentiation of C2C12 cells is also blocked by Deltex over expression, implicating Deltex in this pathway (35). Similar results have been obtained from related experiments examining the inhibition of the bHLH transcription factors E47 and Mash1 by Notch signalling (36, 37). Finally how Notch signalling via Deltex regulates differentiation remains unclear and further experiments will be necessary to resolve the molecular mechanism.

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Abbreviations

CSL	CBF1, Suppressor of Hairless, Lag-1
DSL	Delta, Serrate, Lag-2
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
SOP	sense organ precursor
Su(H)	Suppressor of Hairless
bHLH	basic helix-loop-helix
E(spl)	Enhancer of split
Gro	Groucho
Mcd	microchaete defective
Ax	Abruptex
EGF	epidermal growth factor
LNG	Lin-12, Notch, Glp-1

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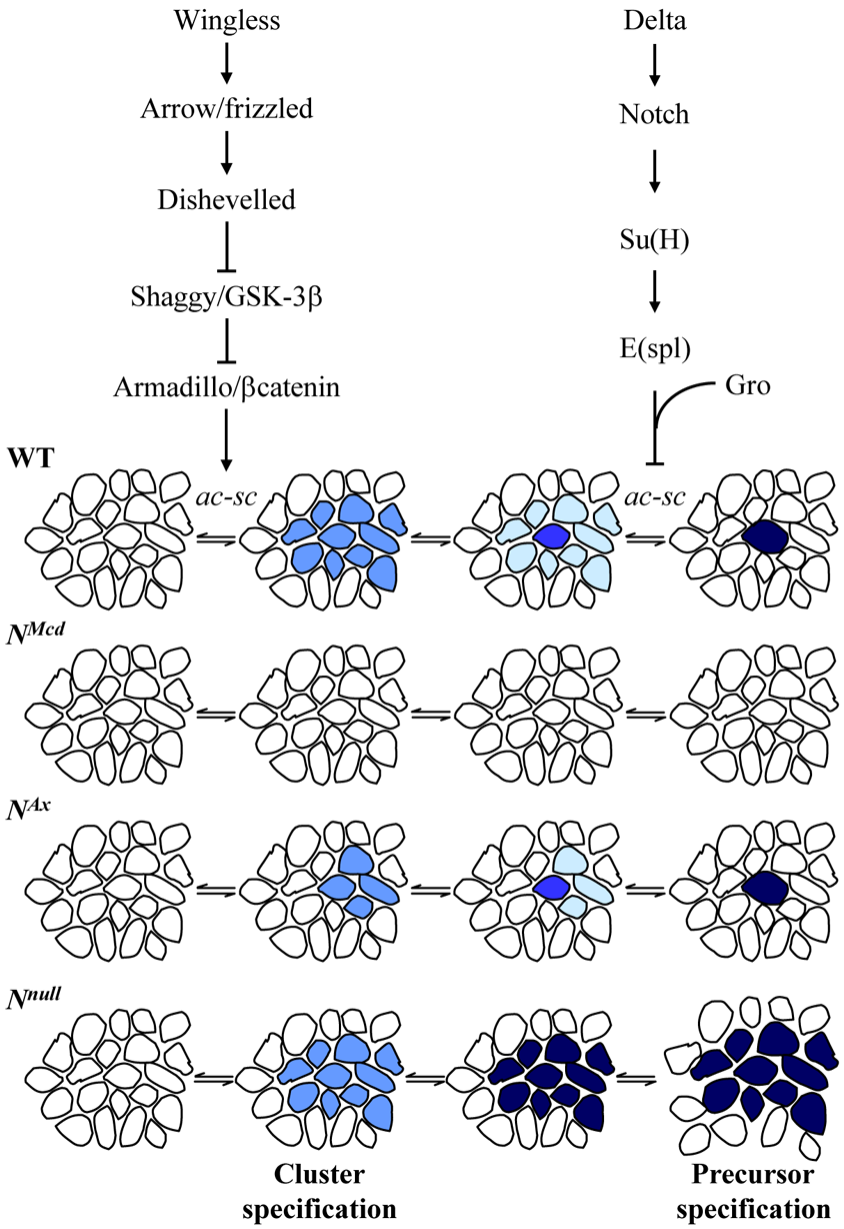

Figure 1. Summary of SOP development in wild type and Notch mutant backgrounds

In wild type flies, the combined action of the prepattern genes and signalling through the Wingless pathway leads to the expression of proneural genes of the *achaete-scute complex* in small groups of cells. All the cells within these proneural clusters have the potential to develop into SOPs. However lateral inhibition signalling restricts *achaete-scute* expression to one or two cells. These cells will divide three times to produce the socket, bristle, supporting, glial and neural cells of the sensory bristles. In the N^{Mcd} and N^{Ax} mutants there is increased Notch signalling via Deltex which represses proneural gene expression. This signalling prevents proneural cluster specification in N^{Mcd} flies and consequently no SOPs develop. In N^{Ax} mutants the increase in signalling via Deltex is not as great and proneural clusters of reduced size develop. The process of lateral inihibition then restricts proneural gene expression to one cell. Both signalling via Deltex and lateral inhibition are abolished in

N^{null} clones leading to robust *achaete-scute* expression and the development of multiple SOPs.

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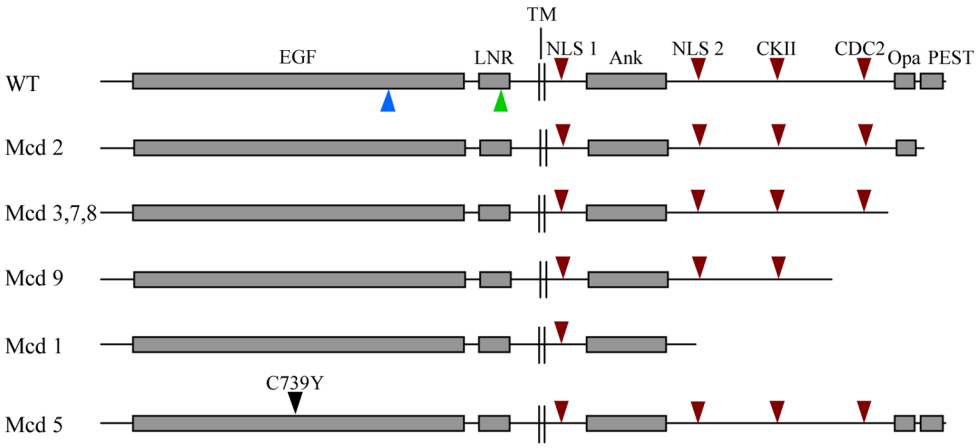

Figure 2. A schematic representation of the Notch protein

The Notch protein contains 36 tandemly repeated epidermal growth factor (EGF) -like and three LNG (Lin-12, Notch, Glp-1) repeats in its extracellular domain. The intracellular domain contains a juxtamembrane RAM23 domain, six cdc10/ankyrin repeats, two nuclear localisation sequences (NLS), caesin kinase II (CKII) and CDC2 phosphorylation sites, a poly glutamine (OPA) repeat and a PEST sequence. The seven different N^{Mcd} proteins are shown below the wild type protein and position of the N^{Ax} and $l(1)N^{B}$ mutations is indicated by blue and green arrowheads respectively.

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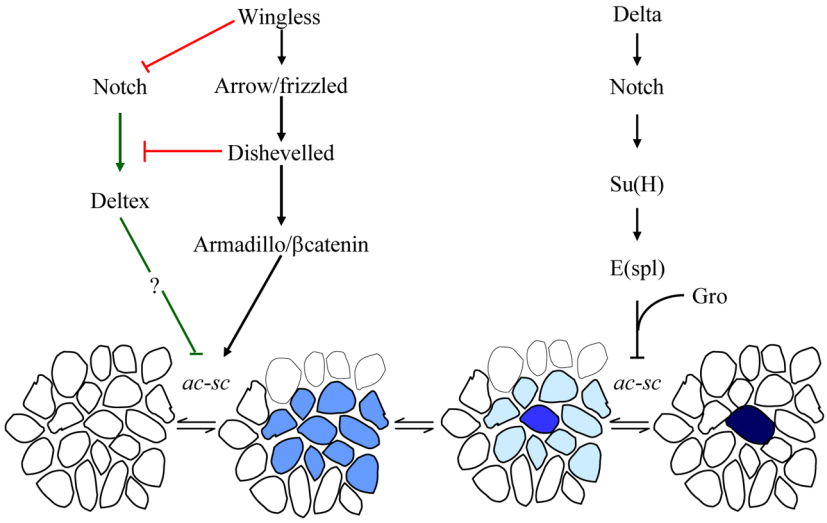

Figure 3. A model for regulation of Notch signalling via Deltex by Wingless signalling

The *achaete-scute* expression is initiated by the combined action of the prepattern genes. However Notch signalling via Deltex represses proneural gene expression. Wingless signalling alleviates this repression locally through the interactions of Dishevelled, Wingless or both with the Notch protein. Inhibition of signalling via Deltex and signalling through the canonical Wingless pathway leads to proneural cluster development from which one or two SOPs will arise.

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