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Recent Advances in Notch Signaling Pathway in Drosophila: A Snapshot

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Abstract

Notch signaling pathway unfolds principal cell communication machinery that plays a vital role in development. It is apparent from several studies that the outcome of Notch signaling is tightly regulated in different cellular context. Notch signaling affects a number of cellular processes at various developmental stages by modulating itself in number of ways to produce different magnitude in the signaling output. It is, therefore, important to understand the context dependent complexity of Notch and various modes of its regulation. This article aims to briefly describe the advances in Notch signaling in Drosophila in the past one year.

Introduction

During the course of evolution, the first multicellular organism is believed to be evolved around one billion years ago though the traces of life dates back to almost 3.5 billion years. One of the reasons for the rather slow rate of evolution lies in the fact that it took a very long time for the cells to develop machinery that would help them behave 'socially'. Signal transduction pathways are one of the important tools that enable cells to communicate easily and decide unique developmental outputs. However, the interesting fact is that there are a handful of core signaling pathways operating in a cell and a cell is engaged in a variety of developmental and physiological constrains at a given time so these signaling systems need to be very precise in delivery and at the same time multifunctional in approach too. To meet these requirements, signal transduction pathways often behave in a context specific manner. Moreover, some of the components of these pathways act as 'adapters' to allow integration of more than one signaling pathways in a specific microenvironment. These 'adapters' may thus affect the output of a single pathway and bring about the gamut of additive or inhibitory effects depending on the developmental requirements.

Notch signaling is one of the most primitive signaling pathways in terms of its discovery. In fact, it has been a century since Notch was first discovered. Studies on mechanisms and regulations of Notch pathway have gained utmost importance over the years and a plethora of information has been generated suggesting the indispensability of the Notch pathway in almost every cellular and developmental context. Since Notch has grown as one of the principal cell fate regulators, studies have revealed a large number of modifiers, which may affect the activation, termination or the duration of the Notch signal. Over the last few years, studies have presented a number of new components, which are involved in transducing the signal from other pathways and also affect the Notch signaling pathway depending on the cellular contexts. Thorough reviews on the mechanism and regulation of Notch signaling can be found elsewhere [1,2]. Here, we aim to provide a brief overview of the recent advancements in Notch signaling in Drosophila over the past one year.

Notch Signaling in Cell Proliferation and Cell Death

Notch often integrates, in a context specific manner, with other signaling pathways to regulate the outcome of proliferation and cell death events. Several studies have outlined the importance of canonical signaling proteins in mediating a functional interaction with components of Notch signaling pathway to modulate the developmental output. However, the complete picture is yet far from being understood. Recently, work of Ho and colleagues identified a novel synergistic relationship between Notch and non-receptor tyrosine kinases Src42A and Src64B. Their studies showed that integration of Notch with these non-receptor tyrosine kinases promoted hyperplasia, tissue disorganization eventually leading to cell cycle perturbation and JAK/STAT signal activation. Interestingly, activation of JNK signaling downstream of N-Src synergy was different from previously identified Notch-Mef2 synergy [3]. This study is important as it suggests how Notch may utilize subtle differences in downstream effectors to modulate a number of signaling pathways, depending on the context, leading to its pleiotropic function.

Another study by Portela and colleagues provides more mechanistic information about interactions between Notch and Lgl. They showed that the overexpression of Lgl could suppress N-ECD (Notch-extracellular domain), but not the N-ICD (Notch-intracellular domain) phenotypes. They further investigated that this did not affect endogenous Notch signaling but depletion of Lgl caused increased ligand-dependent Notch signaling. lgl mutant tissue displayed accumulation of early endosomes, recycling endosomes, early-multivesicular body markers and acidic vesicles. Feeding vesicle de-acidifying drug Chloroquine could rescue the elevated Notch signaling in lgl mutant tissue [4,5]. This study links the Notch endocytosis with its role in tumorigenesis in vivo.

Spratford and Kumar investigated a relationship between Notch and Daughterless (Da) during cell proliferation events in the developing Drosophila eye. They showed that partly Notch signaling was responsible to block the growth-suppressing activity of the bHLH DNA-binding protein Daughterless, in addition to regulating growth-promoting genes such as four-jointed, cyclin D1 and E2f1. They demonstrated that Notch signaling activated the expression of extramacrochaetae (emc), which then formed a heterodimer with Da. This heterodimer cannot bind to and regulate genomic targets, which thus relieve repression on growth [6]. This study is interesting as it suggests how Notch indirectly

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regulates growth repressors, such as Da, apart from directly promoting growth and proliferation.

The role of Notch signaling has been extensively studied till date in many developmental models. Tracy and colleagues revealed that Notch activity was increased in dying Drosophila salivary glands, which was influenced by Ral. Furthermore, decreased Notch function influenced autophagy [7]. Studies by Zimmermann and colleagues described that the Drosophila gene putzig (pzg) was found in a complex together with the nucleosome-remodeling factor NURF. This complex promotes Notch target gene activation. They further showed that down regulation of pzg activity in the developing wing imaginal discs induced apoptosis by activating the pro-apoptotic gene reaper, repression of the Drosophila inhibitor of apoptosis protein accumulation and the activation of the caspases Drice, Caspase3 and Dcp1. They linked down regulation of Notch to the activation Dcp1 caspase and JNK signaling [8]. These studies further provide cues to understand role of Notch signaling in regulating cell death during development.

Role of Notch Signaling in Stem Cell Fate Specification

Adult midgut of Drosophila harbors multipotent intestinal stem cells (ISCs) which produce two types of daughter cells: nutrient-absorbing enterocytes (ECs) and secretory enteroendocrine (EE) cells in response to high and low levels of the Notch ligand Delta (Dl) in ISCs respectively. Guo and Ohlstein reported that during EE cell formation, the EE cell marker Prospero localized to the basal side of dividing ISCs and the EE daughter cell acted as a source of Dl that induced low Notch activity in the ISC after asymmetric division. However, this regulation is bidirectional and ISCs that express Dl can induce high Notch activity in daughter cells to promote EC formation [9]. Okumura and colleagues provided evidences that the Drosophila intestinal GATA factor, GATAe was involved in the differentiation of enterocyte (EC) and enteroendocrine (EE) cells in both Notch (N) -dependent and independent manner. They further suggested that GATAe had an important role in maintaining normal epithelial homeostasis of the Drosophila adult midgut through Notch signaling [10]. Additionally, Lu and others found that though Notch downstream targets E(spl)mbeta and E(spl)malpha were differentially expressed in ISCs, defects in ISC proliferation and differentiation in Notch mutant could not be rescued by ectopic expression of E(spl)mbeta or E(spl)malpha suggesting that proliferation and differentiation of ISCs might not be regulated by individual Notch downstream target, but by different downstream targets in a collective manner [11]. Furthermore, Baechler and others described that transcription factor Hindsight (Hnt) /RREB-1 was required for EC differentiation in the context of ISC to EC differentiation and not for adult midgut precursors (AMP) to EC differentiation in the posterior midgut. Though ISC expression of hnt was not found to be dependent on Notch signaling rather was dependent on Egfr signaling, hnt expression was primarily maintained in ISCs devoid of Notch [12]. A very interesting study by Wang and colleagues demonstrated Ttk69 as a novel repressor of EE cell fate. Loss-of-function of Ttk69 directed all committed progenitor cells to adopt EE fate and gain-of-function of Ttk69 was able to prevent EE cell specification. Importantly, Notch expression in Ttk69-depleted progenitors was not able to prevent EE cell specification suggesting that Ttk69 might function in parallel with Notch signaling and to regulate EE cell specification [13]. These studies have contributed significantly to understanding the role of Notch in ISC proliferation and differentiation.

The hub cells in male germline stem cell niche in Drosophila are specified early by Notch activation. Eventually, before differentiation, they cluster together to a defined position. Wingert and DiNardo described that the large Maf transcription factor Traffic jam (Tj) has an important role in hub cell specification downstream of Notch. They went on to show that the first detectable effect of Notch activation in hub cells was Tj downregulation. However, hub cell assembly downstream of Notch requires a branched pathway with Bowl and Tj downregulation functioning in parallel [14]. Additionally, Jia and colleagues performed an in vivo RNAi screen to identify novel genes involved in follicle cell differentiation where Notch plays a pivotal role. They found a preferential early endocycle entry in anterior follicle cells than those in the posterior and identified that the insulin-PI3K pathway participates in the precise mitotic cycle/endocycle (M/E) switch. They further suggested that Nejire might act as a cofactor of Notch signaling during oogenesis [15]. These studies further provided insights into the role of Notch signaling in germline specification in Drosophila.

Role of Notch signaling in neural stem cell differentiation is also studied extensively though a complete role of Notch in not understood till date. Notch signaling is required in type II neuroblasts during normal development of their transit amplifying progeny known as intermediate neural progenitors (INPs). Work of Farnsworth and others described that aging INPs lose competence to respond to constitutively active Notch signaling. They provided evidences that by reducing the levels of the old INP temporal transcription factor Eyeless/Pax6, Notch signaling could promote the de-differentiation of INP progeny into ectopic INPs [16]. This study presents a new link between Eyeless/Pax6 and Notch signaling during development. Furthermore, work of Arya and colleagues revealed a new role of Notch activity in neural stem cell death. They showed that, in neural stem cells, Notch regulates the expression of the abdominal A homeobox protein, an important spatial signal for death. They also described that pro-apoptotic Notch signaling was activated by the Delta expressing on the neighbouring progeny of the stem cell [17]. This study interestingly provides cues to understand the role of Notch signaling in regulating the neural stem cell death.

An interesting study by Huang and Kornberg described role of specific cytonemes in Wingless (Wg) and Notch signaling to air sac primordium (ASP). They reported that cytonemes additionally link myoblasts to disc cells and to the ASP, thereby allowing myoblasts to transmit signaling between the disc and the ASP. Frizzled (Fz) positive myoblast cytonemes could take up Wingless (Wg) from the disc, and Dl positive myoblast cytonemes lead to Notch activation in the ASP. Furthermore, Wg signaling negatively regulates Dl expression in the myoblasts [18]. This study provides useful information regarding fine-tuning of Wg and Notch signaling during wing disc development.

Role of Notch During Hemocyte Differentiation

Notch signaling plays an important role during hemocyte lineage specification. Work of Ferguson and colleagues described a hierarchy of events in crystal cell differentiation. They suggested that Notch activates Suppressor of Hairless, which in turn leads to activation of Yorkie. Yorkie then interacts with Scalloped to transcriptionally activate Lozenge, which specifies a crystal cell progenitor. The Lozenge positive crystal cell progenitor further turns on Prophenoloxidase to become a mature crystal cell [19]. Another independent investigation of Reimels and Pfleger described a role of Rabex-5 in hemocyte specification. They showed that loss-of-function of Rabex-5 was sufficient to increase hemocyte populations, increase lymph gland size and induce melanotic masses. They also explained that Rabex-5 could negatively regulate Ras, which caused Rabex-5 specific hematopoietic phenotypes and suggested a possibility that Rabex-5 could play a role in cross talk of Ras and notch during Drosophila hematopoiesis [20].

Role of Notch Signaling During Nervous System Development and Memory Formation

Kidd and others investigated how Notch signaling is involved in olfactory receptor neurons (ORNs) during chronic odor exposure. They showed that prolonged odor exposure results in increase in the volume of glomeruli as mainly by Notch activity. By Calcium imaging experiments, they described that apart from its role in structural plasticity, Notch is also essential for the odor induced changes in the physiology of ORNs and the changes in the physiological response of their second order projection neurons (PNs). Both canonical cleavage-dependent and non-canonical cleavage-independent Notch pathways are utilized in ORNs in response to chronic odor exposure and Dl in PNs is responsible for switching the balance between the pathways [21]. Work of Zhang and others described that an increased expression of the full-length Notch receptor (N-FL) could trigger long-term memory (LTM) formation even after very weak training. They reported that increased N-ICD expression couldn't impact LTM formation or suppression. Also, it either does not impact or decreases both the levels and activity of cAMP response element binding protein that is an important factor for supporting LTM [22]. Sturgeon and colleagues conducted a reverse genetic screen for mutations that affected GluR localization at the third instar larval neuromuscular junction (NMJ). They identified Mindbomb1 (Mib1), the E3 ubiquitin ligase, which promotes Notch signaling, as a regulator of synaptic GluR localization. They showed that it could positively regulate the localization of the GluR subunits GluRIIA, GluRIIB, and GluRIIC and levels of Mib1 could affect the structure of the presynaptic motor neuron [23].

Regulations of Notch Signaling at the Levels of Ligands, Receptors and Transcription Factors

To keep a check on the signaling output in various cellular contexts, Notch signaling is tightly regulated at the level of receptor and ligand biosynthesis, post-translational modifications, ligand-receptor interaction and trafficking. Work of Chou and colleagues has identified the role of Breast Carcinoma Amplified Sequence 2 (BCAS2) in Delta pre-mRNA splicing. They further showed that dBCAS2 depletion reduced the Delta mRNA expression and transcription of Notch target genes, cut and E(spl) m8. Ectopic expression of human BCAS2 (hBCAS2) and Drosophila BCAS2 (dBCAS2) in a dBCAS2-deprived fly could rescue dBCAS2 depletion-induced wing damage associated with the Delta pre- mRNA splicing. Overexpression of Delta can rescue the wing deformation by depletion of dBCAS2 and loss of dBCAS2 can restore the eye phenotypes associated with Delta-overexpression [24]. This study identifies BCAS2 as a novel Dl ligand regulator in Drosophila. Additionally, Ishio and colleagues have shown that O-fucose modification of Notch has a temperature-sensitive function important for Notch signaling [25]. Contreras and others described the assembly of the Drosophila ternary complex using isothermal titration calorimetry. Their study reveals fly specific interaction of RAM (RBP-J associated molecule) and ANK (ankyrin) domains of N-ICD with CSL transcription factor. Moreover, they further suggested that the binding of the Drosophila RAM domain to CSL did not affect interactions of the co-repressor Hairless with CSL transcription factor [26]. Auer and colleagues have shown that Su(H) is phosphorylated in response to MAPK activity which attenuates Notch signaling [27]. These studies highlighted the regulation of Notch signaling at the level of ligand, receptor and transcription factor in Drosophila and its conservation across species.

Endocytic Trafficking

Endocytosis has long been recognized as one of the ways for signal attenuation however; many advance studies have provided insights into its role in multiple steps during signal transduction. Recent work of Tognon and colleagues has described a role of Mitf (the single TFEB and MITF ortholog in Drosophila) in regulation of Notch endo-lysosomal localization. They showed that modulating the activity of Mitf in wing imaginal disc altered endo-lysosomal function and disrupted the proneural patterning in the disc. Thus, this study highlights the role of Mitf in ligand independent Notch signaling [28].

Novel Modulators

Recently, many new components have been added to the Notch signaling pathway and attempts are made to pinpoint their precise role in regulation of Notch signaling. These studies help in explaining why there are so many modulators of a single signaling pathway and why Notch utilizes a specific component depending on a distinct developmental requirement. Furthermore, some of the regulators have evolved during the course of specific evolutionary needs of the signal. Multicellular organisms utilize a set of Notch pathway receptors and ligands and these modifiers tend to show affinity to a subset of Notch ligands or receptors. A handful of new regulators of Notch signaling have been identified during past one year. Our own study on Drosophila Misshapen (msn) identifies it as a new regulator of Notch signaling. We have shown that the kinase active form of Msn exhibits phenotypes similar to Notch loss-of-function condition and msn genetically interacts with components of the Notch signaling pathway. Moreover, we further showed that active Msn could associate with the Notch receptor and regulate its signaling. Interestingly, we observed that kinase active Misshapen leads to accumulation of membrane-tethered form of Notch [29]. This study provides a very important cue to understand how Notch could associate with the components of other signaling pathways and this affects Notch signal activity. In a similar manner, we have earlier shown that Drosophila TRAF6 also associates with the Notch receptor and regulates its signaling [30].

We have also identified a couple of other interactors as regulators of Notch signaling. Work of Surabhi and others showed that ectopic expression of Maheshvara (mahe), a putative DEAD box helicase protein, resembles a typical Notch loss-of-function phenotype and leads to loss of Notch targets, Cut and Wingless. Additionally, mahe overexpression could significantly rescue ectopic Notch-mediated proliferation in the eye. Co-expression of Mahe and another Notch modulator Deltex resulted in wing-nicking phenotype and a more significant loss of Notch target Cut [31]. Furthermore, we have also identified Chip as another interactor of Notch. We reported that Chip (Chi) and Notch interact physically and genetically. Moreover, Chi mutant clones in the dorsal compartment of the wing disc induced ectopic wing margins by ectopic expression of Notch and its targets, Wg and Cut. Our results indicated that the stoichiometry of Notch and Chip was critical at the dorso-ventral (DV) boundary for wing margin formation. Additionally, overexpression of Chip could rescue Notch-induced cell proliferation in larval imaginal discs [32]. Han and colleagues have further investigated that differential Chi protein levels in adjacent cells could activate Notch signaling chiefly in the cells with a higher level of Chi protein [33]. Works of Fiedler and others have further showed that Chip/LDB-SSDP (ChiLS) complex provides context-dependence on TCF/LEF by integrating several inputs from a number of factors, including enhanceosome switch-off by Notch [34]. All these studies have provided a broad mechanistic overview of previously unknown functions of chip in Notch signaling.

Conclusion

It is very important for a cell to maintain signaling homeostasis and several novel mechanisms towards this end have been understood till date yet the complete and thorough understanding of the total picture demands further investigation. Notch is very dosage sensitive and its function is highly pleiotropic in nature. Pleiotropic actions of Notch in different cell types are results of regulation of its signal activation, longevity and termination at multiple levels. As a large number of cellular processes are dependent on Notch signaling for their correct culmination, aberrant Notch signaling is a major cause of several human diseases including carcinogenesis. In recent years, more emphasis has been given to identification of novel candidates that are involved in many other signaling pathways and also modulate Notch signaling. Furthermore, the modulators that can affect the signaling output by posttranslational modifications or endocytic trafficking of Notch receptor or the other components of the Notch pathway are also being investigated extensively. This would enrich our current understanding of mechanisms and functions of Notch signaling in various developmental contexts.

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