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# Crossing paths with Notch in the hyper-network

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The development of complex and diverse metazoan morphologies is coordinated by a surprisingly small number of evolutionarily conserved signaling mechanisms. These signals can act in parallel but often appear to function as an integrated hyper-network. The nodes defining this complex molecular circuitry are poorly understood, but the biological significance of pathway cross-talk is profound. The importance of such large-scale signal integration is exemplified by Notch and its ability to cross-talk with all the major pathways to influence cell differentiation, proliferation, survival and migration. The Notch pathway is, thus, a useful paradigm to illustrate the complexity of pathway cross-talk: its pervasiveness, context dependency, and importance in development and disease.

## Addresses

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## Introduction

Metazoans rely on a handful of core signaling mechanisms to guide a wide range of developmental processes, from the earliest specification events to organogenesis. Key among these are the Hedgehog (Hh), Janus kinase/signal transducers and activators of transcription (Jak/STAT), nuclear receptor, receptor tyrosine kinase (RTK), transforming growth factor- $\beta$ /Decapentaplegic (TGF- $\beta$ /Dpp), Wnt/Wingless (Wnt), and Notch (N) pathways [1–4]. Together, these highly conserved pathways create a signaling backbone supporting all stages of metazoan development [1–4]. It is remarkable that metazoan species, despite being constrained to this shared signaling framework, have managed to evolve into species of vastly diverse body plans [5••].

To achieve the morphological complexity that is characteristic of metazoans, these core signaling pathways must integrate to form a larger, complex signaling system, which we term the hyper-network. However, comprehensive knowledge of this network, the nodes that define it and its emergent properties is lacking. Studying how these highly pleiotropic pathways are interlinked is essential to understanding development and evolution and, consequently, defines a fundamental problem in biology with obvious implications for disease.

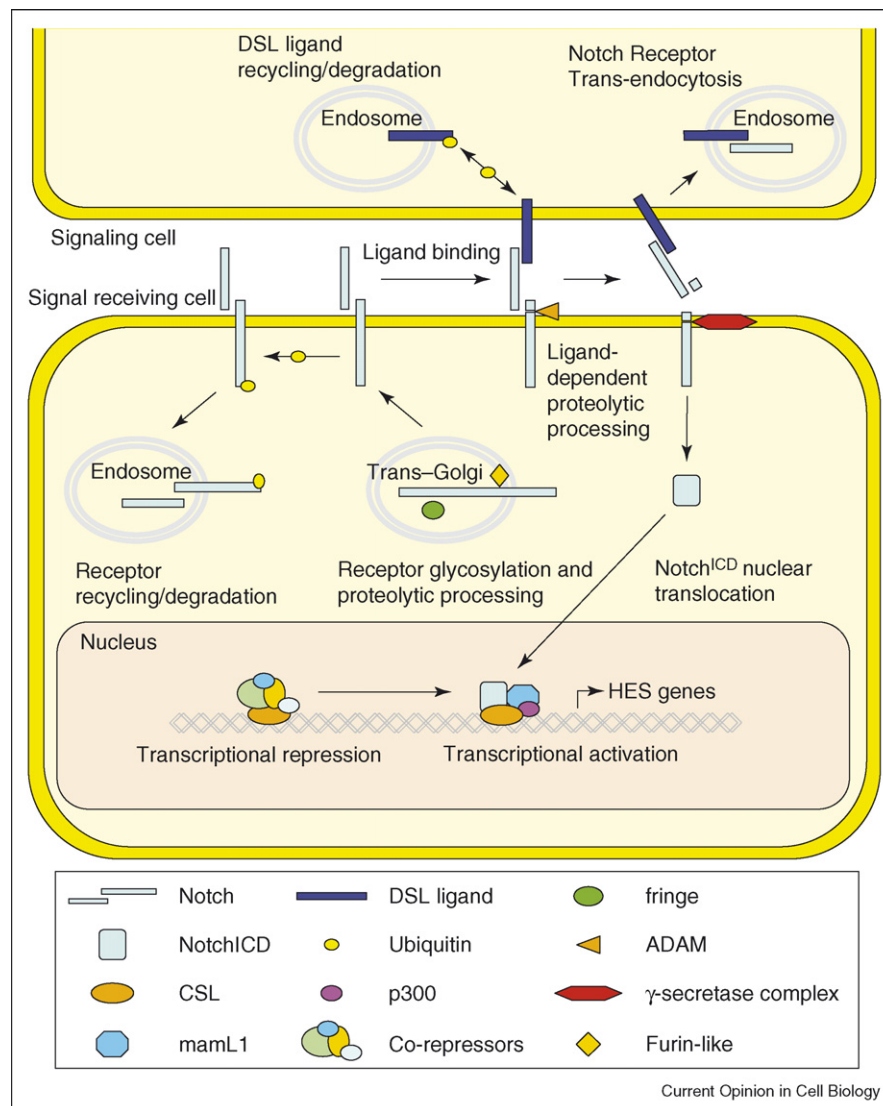
Given the pleiotropy of Notch signaling, its importance to development and disease [6••,7–10], and its ability to integrate with all major pathways (see below and Figure 1), in this review we focus on Notch signal integration, or ‘cross-talk’. We aim to provide a brief perspective on this signaling hyper-network and illustrate the importance of cross-talk, its pervasiveness, and its capacity to generate complexity during development.

Metazoans share common functional and mechanistic aspects of Notch signaling, which have been outlined in several recent reviews [6••,7–10]. Notch signaling involves receptor activation by a membrane-bound Delta/Serrate/Lag-2 (DSL) ligand, leading to proteolytic processing of the receptor (Figure 1). This releases the central signaling molecule, the Notch intracellular domain (N<sup>ICD</sup>), which undergoes nuclear translocation and association with a CBF1/Su(H)/Lag-1 (CSL) family transcription factor, promoting expression of E(spl)/HES family and other target genes [11]. Ultimately, Notch signaling affects cell-fate specification, proliferation, apoptosis and migration. Aberrant Notch signaling has been associated with pathogenic conditions including carcinogenesis. Very few studies have been specifically designed to address pathway cross-talk; however, numerous links between Notch and other signaling pathways have emerged (Figure 2). Undoubtedly, Notch cross-talk is pervasive in development and contributes to the astounding spectrum of Notch function (Table 1).

## Cell-fate specification

Cross-talk has an important and prevalent role in cell-fate specification. As exemplified by Notch/RTK integration, the influence of cross-talk on cell fate appears to be complex, and, in different contexts, integration can have agonistic or antagonistic effects. Antagonism predominates during *C. elegans* vulval development and in some aspects of *Drosophila* photoreceptor development. In both these cases, Notch opposes RTK-mediated induction of differentiation [12–15]. In *Drosophila*, such antagonism is

Figure 1

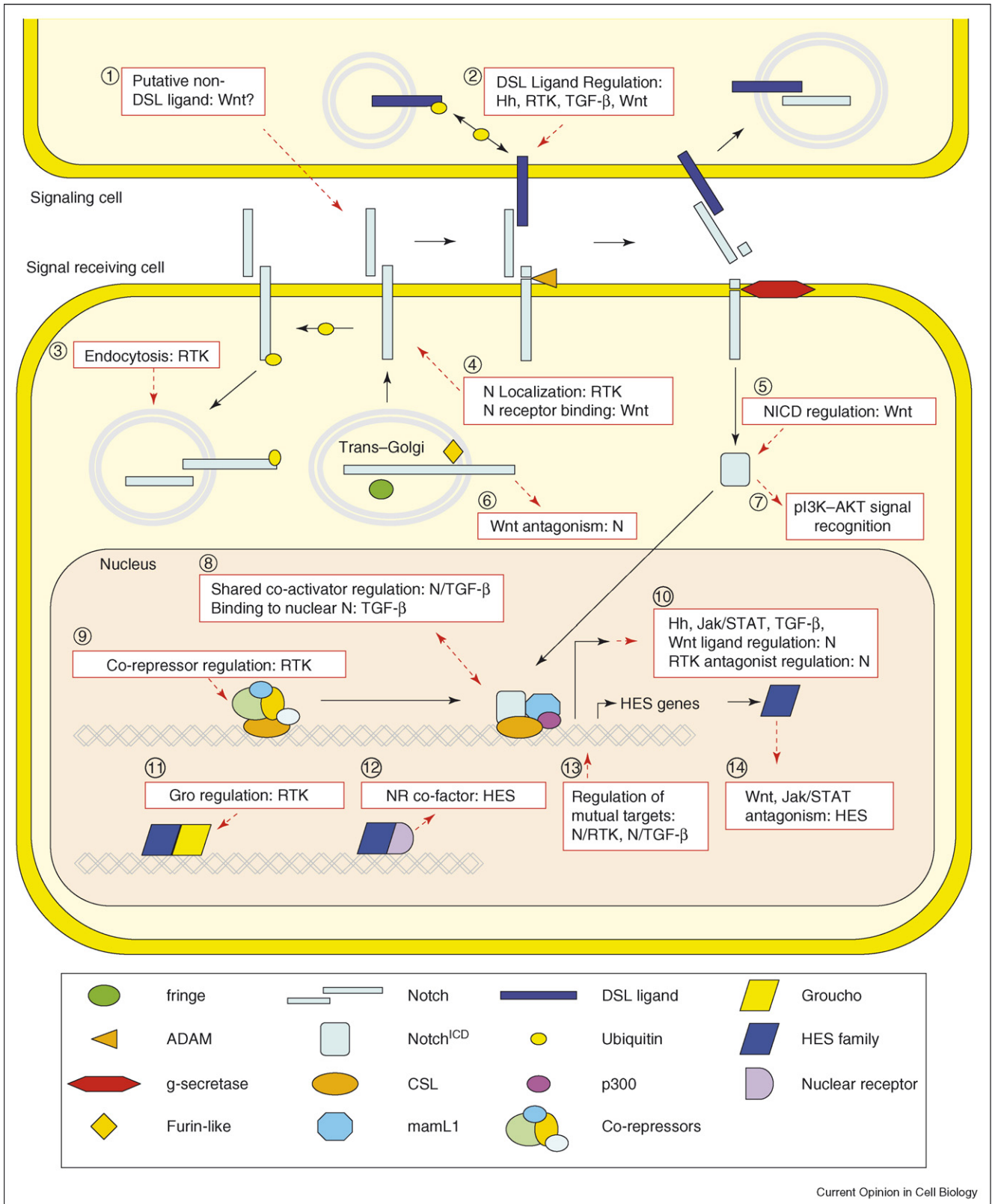


A current overview of Notch signal transduction. The Notch pathway mediates regulation of a diverse array of cell-fate decisions through juxtacrine signaling. Notch receptors are composed of an extracellular domain ( $N^{ECD}$ ) containing numerous  $Ca^{2+}$ -binding EGF-like repeats, a small transmembrane region ( $N^{TM}$ ), and an intracellular domain ( $N^{ICD}$ ) that can act as a nuclear effector. In the ER and Golgi,  $N^{ECD}$  is modified by a series of glycosylation events mediated by Fringe and other glycosyltransferases. In the *trans*-Golgi, Notch undergoes proteolysis by a furin-like convertase, generating a glycosylated, presumably divalent-cation-stabilized Notch heterodimer. In *Drosophila*, two DSL ligands, *Delta* and *Serrate*, activate signaling. In mammals, ligands include members of the Delta-like (DLL1, DLL3, DLL4) and Jagged (JAG1, JAG2) families. Upon ligand binding,  $N^{ECD}$  is removed through cleavage by an ADAM metalloprotease, TNF- $\alpha$  converting enzyme (TACE).  $N^{ECD}$  remains bound to the ligand, and both proteins may be endocytosed by the ligand presenting cell. The physical force generated by this ligand/ $N^{ECD}$  internalization may be required for receptor cleavage by TACE, and further receptor processing required for signaling. Upon cleavage by TACE, constitutive cleavage events mediated by the  $\gamma$ -secretase complex release  $N^{ICD}$ . The  $N^{ICD}$  translocates to the nucleus and associates with a *CBF1/Su(H)/Lag-1* (CSL) family transcriptional regulator. In the absence of  $N^{ICD}$ , CSL family proteins are part of a repressor complex. Upon Notch binding, co-repressors are exchanged for co-activators, including Mastermind and p300, leading to the activation of target genes, including HES family members. Both the Notch receptor and its ligands can undergo ubiquitin-regulated internalization and degradation. We note that several aspects of this overview reflect a working hypothesis and some aspects are not necessarily rigorously proven. This is especially true for aspects of receptor and ligand trafficking and the exact sub-cellular localization of the cleavage events.

crucial to specification in numerous other contexts [14–17]. Though, canonically, Notch signaling maintains an undifferentiated cell fate, in many contexts Notch is actually required to direct specification events, and here

the effects of cross-talk may also be important. For example, in the *Drosophila* eye, in addition to the pathway antagonism observed in photoreceptor development, Notch and RTK act cooperatively to specify accessory

Figure 2



For an overview of Notch signaling see Figure 1. Nodes of integration are indicated by text in numbered red boxes and references for the data in each is listed next to its corresponding number below. Some of the indicated modes of cross-talk, including the role of wingless as a

cells [14,18,19]. Such variable effects of Notch pathway cross-talk on cell-fate specification and its context dependency seem to be the rule rather than the exception.

Like Notch/RTK cross-talk, the effects of signal integration with Wnt on cell fate vary with context. During vertebrate osteoblastogenesis, ST-2 stromal cells differentiate as osteoblasts when treated with Wnt3a. In the presence of ectopic Notch1<sup>ICD</sup>, however, these cells undergo adipogenesis. Thus, in this context, the effect of Notch on Wnt signaling is antagonistic [20<sup>\*</sup>]. In contrast, pathway synergy is observed in the adult mouse epidermis, where Notch and Wnt/ $\beta$ -catenin cooperate to maintain postnatal hair growth. If either signal is blocked, hair follicles convert into cysts of interfollicular epidermis, while simultaneous activation of both pathways increases induction of ectopic hair follicles [21]. Osteoblastogenesis is also influenced by Notch/TGF- $\beta$  cross-talk, where cooperation between Notch1 and the TGF- $\beta$  ligand BMP-2 promotes differentiation [22]. During myogenesis, however, Notch and BMP-4 synergize to inhibit differentiation [23]. The opposing influence of cross-talk on cell fate in different contexts thus appears to be a common theme, suggesting that flexible integration is an essential feature of the hyper-network.

### Proliferation and apoptosis

Notch, classically associated with cell differentiation, has also been shown to direct cells into proliferative or apoptotic states. Interestingly, Notch has both cell-autonomous and non-cell-autonomous effects on mitotic activity, which in different contexts it can either promote or suppress. Though many aspects of Notch signaling in proliferation and apoptosis remain poorly understood, its potential to link these events with differentiation may be of particular relevance to dysproliferative states, including cancer. Again, developmental context appears to dictate how Notch activation affects the cell cycle. The logic of integration appears complex, as Notch signals can have either oncogenic or tumor-suppressive effects in tumors of the same type (see below). As with differentiation, this complexity may depend upon cross-talk.

To date, three distinct signaling pathways, Jak/STAT, RTK and Wnt, have been shown to affect proliferation, in part through integration with Notch. At the dorsoventral boundary (DV) of the *Drosophila* eye primordium, where Notch activation plays a crucial role regulating eye growth and patterning [24<sup>\*</sup>], ectopic Notch activation induces dramatic proliferation through a non-cell-autonomous

mechanism that involves activation of Jak/STAT signaling through its ligand *unpaired* [24<sup>\*</sup>–26<sup>\*</sup>]. In the *Drosophila* wing disc, where multiple signals influence growth during development [27], the Notch and RTK pathways can synergize to promote dramatic overgrowth (Hurlbut and Artavanis-Tsakonas, unpublished). Cross-talk with Wnt/wingless also influences wing growth. Notch/Wnt integration induces proliferation in cells of the wing pouch and hinge [27] but cell-cycle arrest in those that form the wing margin sensory organs [28]. As Notch/Wnt integration regulates early precursor cell proliferation in mouse intestinal crypts [29<sup>\*\*</sup>,30] the importance of such cross-talk in proliferation appears to be functionally, if not mechanistically, conserved.

Notch signals have been shown to influence cell death in both vertebrates and invertebrates. The influence of cross-talk on this process is evident in the *Drosophila* eye, where, during late pupal development, Notch provides a pro-apoptotic cue that opposes RTK-dependent survival [31]. Demonstrating the significance of cross-talk, in the absence of RTK signaling through the EGFR receptor, Notch is no longer required for apoptosis. By contrast, Notch and Wnt/wingless act together to promote apoptosis during earlier stages, where signaling through EGFR appears not to be involved [32]. Highlighting the importance of context, wingless opposes a Notch pro-apoptotic signal in the *Drosophila* wing [27].

### Stem cells

Stem cell maintenance, crucial to regeneration, requires signaling. Given the potent ability of Notch to influence cellular differentiation, it is not surprising that Notch signaling has emerged as an important regulator of stem cells of the mammary gland, eye, skin, nervous system, bone marrow, stroma, gastrointestinal (GI) tract and ovary [33]. Often, Notch integration with other signaling pathways plays an essential role, with Notch/Wnt cross-talk being of particular importance. In both the GI tract [34] and early hematopoiesis [35<sup>\*\*</sup>], Notch and Wnt influence stem/precursor cell maintenance and, perhaps, proliferative potential, through their cooperative effect. In some contexts, stem cell survival may depend on Notch integration with multiple pathways. In murine somatic and human embryonic stem cells, Notch signaling activates the p13K/Akt/mTOR pathway, leading to specific phosphorylation of the Jak/STAT mediator STAT3 at serine residue 727, which induces expression of target genes including Sonic Hedgehog (Shh), and promotes stem cell survival. This positive survival signal is opposed by

(Figure 2 Legend Continued) Notch ligand, are currently controversial. Dashed arrows provide the direction of influence. Arrows pointing to Notch pathway components indicate that the pathway(s) shown has an effect on Notch signaling, Box 2 [18,60,74–76], Box 3 [77<sup>\*\*</sup>,78], Box 4 [77<sup>\*\*</sup>,78–80], Box 5 [79], Box 9 [76], Box 13 [18,23,70,81–85]. Those pointing away indicate an effect of Notch on the pathway(s) listed, Box 6 [86], Box 7 [36<sup>\*\*</sup>,87], Box 10 [24<sup>\*</sup>,36<sup>\*\*</sup>,66,73,88<sup>\*\*</sup>,89], Box 14 [20<sup>\*</sup>]. Double headed arrows, Box 1 [90], Box 8 [81,91,92], indicate mutual influence specific to the component or process listed. Also shown in the nucleus, is the influence of RTK signaling on the HES co-repressor Groucho, Box 11 [93<sup>\*</sup>], and the influence of Notch signaling on the Nuclear Receptor pathway (NR) by Notch targets of the HES family, which can serve as Nuclear Receptor co-factors, Box 12 [94].



Table 1

## The biological contexts of Notch cross-talk.

Pathway	Species	Context	Process/function	References
Hh	<i>D. melanogaster</i>	Eye	Cooperate in eye development	[74]
Hh	<i>D. rerio</i>	Vasculature	Artery/vein cell specification (with VEGF)	[95]
Hh	<i>H. sapiens</i>	Meduloblastoma	Promote tumor growth and survival (with Wnt)	[59,60]
Jak/STAT	<i>D. melanogaster</i>	Eye	Cooperatively promote growth	[24*–26*]
Jak/STAT	<i>D. melanogaster</i>	Foregut	Cooperatively govern development	[96]
Jak/STAT	<i>D. melanogaster</i>	Oogenesis	Specify stalk and pre-polar cell fate	[97–99]
Jak/STAT	<i>H. sapiens, M. musculus</i>	Embryonic and somatic stem cells	Stem cell survival	[36**]
Jak/STAT	<i>M. musculus</i>	Central nervous system	Cooperate in astrocyte differentiation	[100*]
Jak/STAT	<i>M. musculus</i>	Neural stem cells	Specify stem cell survival versus differentiation	[36**]
RTK	<i>C. elegans</i>	Vulva	Specify vulval cell fates	[13]
RTK	<i>D. melanogaster</i>	Chordotonal organ	SOP fate specification	[17]
RTK	<i>D. melanogaster</i>	Eye	Photoreceptor and accessory cell specification	[14]
RTK	<i>D. melanogaster</i>	Eye/Antenal disc	Specify eye versus antennal identity	[101]
RTK	<i>D. melanogaster</i>	Mesoderm	Specify muscle cell subtypes	[18]
RTK	<i>D. melanogaster</i>	Notum Bristles	SMC fate specification	[16]
RTK	<i>D. melanogaster</i>	Trachea	Specify fusion cell fate	[64]
RTK	<i>D. melanogaster</i>	Wing	Specify wing vein versus intervein	[102]
RTK	<i>D. melanogaster</i>	Wing	Cooperatively promote growth	Unpublished
RTK	<i>D. rerio</i>	Vasculature	Artery/vein cell specification (with Shh)	[95]
RTK	<i>H. sapiens</i>	Cell migration	Notch blocks Ras induced migration in culture	[56]
RTK	<i>H. sapiens</i>	Oncogenesis	Act cooperatively in transformation or growth	[53,55]
RTK	<i>H. sapiens</i>	Thymocyte development	T-Cell lineage specification (Notch and TCR)	[103]
RTK	<i>H. sapiens</i>	Tumor angiogenesis	Cooperatively promote angiogenesis	[104]
RTK	<i>M. musculus</i>	Embryonic segmentation	Cooperatively regulate segmentation clock	[105]
RTK	<i>M. musculus</i>	Spinal cord development	Maintenance of the caudal neural plate	[106]
RTK	<i>M. musculus</i>	Neurogenesis	Promote radial glial identity	[107]
RTK	<i>M. musculus</i>	Oncogenesis	Cooperation or antagonism	[54,56,57]
RTK	<i>M. musculus</i>	Pancreatic tumorigenesis	Cooperate in pathogenesis	[58]
TGF- $\beta$	<i>D. melanogaster</i>	Germline stem cells	Maintenance of stem cells and stem cell niche	[37]
TGF- $\beta$	<i>D. melanogaster</i>	Trachea	Specify fusion cell fate	[66]
TGF- $\beta$	<i>D. rerio</i>	Cardiac development	Promote Epithelial-to-mesenchymal transition	[108]
TGF- $\beta$	<i>M. musculus</i>	Embryonic endothelial cells	Regulation of migration	[70]
TGF- $\beta$	<i>M. musculus</i>	Endothelial migration	Notch blocks TGF- $\beta$ induced migration in culture	[70]
TGF- $\beta$	<i>M. musculus</i>	Muscle	Cooperatively inhibit myogenic differentiation	[23]
TGF- $\beta$	<i>M. musculus</i>	Neurogenesis	Cooperatively inhibit neuroepithelial differentiation	[81]
TGF- $\beta$	<i>M. musculus</i>	Osteoblastogenesis	Cooperatively promote differentiation	[22]
TGF- $\beta$	<i>M. musculus</i>	Prostate gland	Regulation of branching morphogenesis	[68]
TGF- $\beta$	<i>M. musculus</i>	Prostate gland	Regulates epithelial bud formation	[68]
Wnt	<i>D. melanogaster</i>	Epidermis	Interact genetically in this context	[109,110]
Wnt	<i>D. melanogaster</i>	Trachea	Specification of fusion cell fate	[67]
Wnt	<i>D. melanogaster</i>	Wing	Cooperatively regulate development	[80,86,109,111–114]
Wnt	<i>D. melanogaster</i>	Wing margin sensory organs	Cooperatively induce cell cycle arrest	[28]
Wnt	<i>D. melanogaster</i>	Wing Pouch and Hinge	Cooperatively promote growth	[27,115]
Wnt	<i>H. sapiens</i>	Mammary duct morphogenesis	Antagonistically regulate branching	[69]
Wnt	<i>H. sapiens</i>	Meduloblastoma	Promote tumor growth and survival (with Hh)	[60]
Wnt	<i>H. sapiens</i>	Melanoma	Promote tumor growth and metastasis	[61]
Wnt	<i>M. musculus</i>	Epidermis	Cooperate in postnatal hair follicle induction	[21]
Wnt	<i>M. musculus</i>	Gastrointestinal tract	Cooperatively regulate stem cell proliferation	[30,34]
Wnt	<i>M. musculus</i>	Hematopoietic stem cells	Stem cell maintenance	[35**]
Wnt	<i>M. musculus</i>	Osteoblastogenesis	Specify cell fate	[20*]
Wnt	<i>M. musculus</i>	Somites	Cooperate in somitogenesis	[75]

signaling through Jak/p38-MAPK, downstream of ciliary neurotrophic factor (CNTF), which counters Notch-responsive STAT3 phosphorylation at serine 727. This signal instead promotes STAT3 phosphorylation at tyrosine residue 705 and, ultimately, cell differentiation [36\*\*]. In the *Drosophila* ovary, maintenance of germline stem cells (GSCs) requires a Notch/TGF- $\beta$  signal feedback loop. Loss of either signal leads to GSC differentiation

and exit from the stem-cell niche [37\*]. Dysregulation of the stem cell self-renewal process, which involves regulation of apoptosis, proliferation and differentiation, may be a significant event in the genesis of certain cancers. Indeed, it is speculated that blocking this process may be a useful therapy [38]. This might be achieved by targeting the nodal points of signal integration, thus modulating the effects of cross-talk.

## Oncogenesis

In normal tissues, proliferation, differentiation and apoptosis exist in delicate balance, and it is the disturbance of such homeostasis that commonly underlies oncogenesis. Given the fundamental importance of signaling in the regulation of these processes, it is not remarkable that disruptions in all major signaling pathways, including Notch, have been associated with oncogenesis [39–49]. Notch, initially linked to cancer through its frequent mutation in T-Cell acute lymphoblastic leukemia [50,51], can, in some tumor-types, integrate with other pathways to affect the course of oncogenesis profoundly. However, the observed effects of cross-talk are often complex and context-dependent. For example, Notch signaling has been shown to either enhance [52–55] or suppress [56,57] the transformation and proliferation of tumors in which RTK is activated. Such inconsistencies are likely to reflect differences in the underlying signal integration in these tumors or associated contexts. In pancreatic tumorigenesis, EGFR signaling may act, in part, to induce Notch activation. Here, cooperation between these pathways may be important to pathogenesis [58]. In human and murine medulloblastoma, Notch and Shh synergize to promote tumor proliferation and survival [59]. In fact, in medulloblastomas, Shh-dependent tumor growth and survival involves synergy with both Notch and Wnt [60]. Notch/Wnt cross-talk has also been suggested to be of importance to melanoma. Activation of Notch1 enhances primary melanoma cell growth and the potential for metastasis through  $\beta$ -catenin upregulation [61]. It is clear that manipulating Notch activity can modify cell fate, and, as first speculated over a decade ago, this capacity makes Notch a therapeutic target of potentially great significance [62]. As evidenced by the different impacts of Notch/RTK integration on tumorigenesis, the effects of Notch manipulation are difficult to predict *a priori*. As a result, a substantial knowledge of the signaling hyper-network underlying a targeted tumor may be necessary for optimal therapy.

## Branching morphogenesis/migration

Networks of branched, tube-like structures, found in metazoan organs of numerous types, are formed through precise regulation of cell differentiation, proliferation, apoptosis, adhesion and migration. Notch is among the many signals crucial to branching morphogenesis, and here cross-talk has also been documented to be important. During *Drosophila* tracheal development, cross-talk between Notch and the Wnt/wingless, TGF- $\beta$ /Dpp and RTK/FGFR pathways generates branch patterning through the cooperative specification of cell fate [63–67]. In vertebrates, Notch cross-talk functions in epithelial bud formation and branching of the developing prostate gland [68]. Specifically, Notch/TGF- $\beta$  antagonism helps regulate prostate branching, while TGF- $\beta$  signaling, activated by the BMP-7 ligand, limits Notch activation, and the epithelial bud formation it promotes,

to subsets of cells within the urogenital epithelium. Cross-talk is also evident in the developing mouse mammary gland, where Notch4-mediated inhibition of branching is overcome by Wnt1 activation [69].

The influence of cross-talk on cell migration has been observed in MDCK and MDA-MB-435 cells, where expression of constitutively active Notch4 blocks hepatocyte growth factor (HGF)-induced Ras activation and cell migration [56]. Additionally, when murine embryonic endothelial cells are in contact, ligand-dependent Notch signaling is activated, and BMP/TGF- $\beta$ -mediated migration is inhibited [70]. This mechanism linking migration to contact through cross-talk may be of crucial importance both in development and in the pathology of numerous diseases.

## Conclusions

The pleiotropy observed for Notch signaling during development is in large part dependent on the ability of context to influence its activity. The basic features of Notch signaling may have emerged by the Precambrian era [71,72] and, as new metazoan species evolved, Notch signaling seems to have retained a central role in development: coupling the fate choices of adjacent cells. However, the mechanisms regulating the Notch signal in different developmental contexts did not necessarily remain invariant during evolution. During development, Notch activity is modulated through the regulation of ligand availability, Notch pathway component transcription and trafficking, and post-translational modification of both the receptor and its ligands. The capacity for modulation at multiple levels may allow other signals and additional context-dependent factors to converge with Notch at numerous points. Supporting this, known mechanisms of signal integration involve nodal points at each step of Notch signal transduction (Figure 2).

It is important to note that cross-talk does not require synchronous signals, as sequential signals can also integrate. Sequential integration can affect progenitor cells that are maintained by Notch and specified by subsequent signals. The mutual influence that pathways can exert on each other through the regulation of ligands is another example of sequential integration. Here, the effects of cross-talk can be non-cell-autonomous. In different contexts, the output of Notch signaling includes the Hh, Jak/STAT, TGF- $\beta$ /Dpp and Wnt pathway ligands [24,36,66,73]. Reciprocally, Notch ligands are an output of Hh, RTK, TGF- $\beta$ /Dpp and Wnt/wingless signaling [18,60,74–76]. This suggests that feedback loops represent important interlinking mechanisms that help turn separate signals into a network. Though soluble Notch ligands have been observed in *C. elegans*, it is noteworthy that Notch signaling is unique in its general requirement for direct membrane-membrane contact. Integration with Notch might, therefore, be a useful

method for pathways activated by diffusible ligands to gain spatial resolution. As such, Notch may play a prominent role in bridging major pathways.

Through either a direct interface between pathways or shared target sets, signal integration might allow a simple interconnected system to generate an extraordinarily diverse output. The dramatic range of morphologies that these few signals can create supports this notion. Studying its effects on the transcriptional output of integrated signals may be a useful approach to understanding cross-talk. Extrapolating from the Notch cross-talk paradigm, several features of the signaling hyper-network can be inferred. First, signaling pathways are remarkably interlinked and can integrate at the cellular and multicellular level through multiple mechanisms. Second, cross-talk is of broad importance, impacting numerous pathway functions, and its dysregulation appears profoundly important to cancer, and potentially to other diseases. Third, cross-talk is flexible, differing in consequence in different contexts. The unknown source(s) providing this specificity are of fundamental importance. As multiple mechanisms interlink diverse signaling pathways with Notch, it is possible that the flexible nature of cross-talk depends upon the primary mechanism employed in each context, but a wide range of factors may also be involved, including additional cross-talk.

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