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Cell death in development: signaling pathways and core mechanisms

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Summary

Programmed cell death eliminates unneeded and dangerous cells in a timely and effective manner during development. In this review, we examine the role cell death plays during development in worms, flies and mammals. We discuss signaling pathways that regulate developmental cell death, and describe how they communicate with the core cell death pathways. In most organisms the majority of developmental cell death is seen in the nervous system. Therefore we focus on what is known about the regulation of developmental cell death in this tissue. Understanding how the cell death is regulated during development may provide insight into how this process can be manipulated in the treatment of disease.

Keywords

cell death; apoptosis; *Drosophila*; development; Hox; Notch; Ras

1. Introduction

Cells die throughout the lifespan of multicellular organisms, and this physiologic cell death is critical for developmental plasticity and for organismal health [1]. In this review we describe the general functions of developmental cell death, focusing on nervous system development. The core cell death pathways that contribute to the majority of developmental cell death will be introduced, and the upstream regulation of these pathways in the context of the developing organism will be discussed.

2. The canonical pathway of cell death

Genes important for apoptosis are highly conserved from worms to man, and include the caspases, and their regulators (Fig. 1). The control of caspase activity is central to the regulation of developmental death. Caspase activity can be controlled by regulating both activation and inhibition. The relative importance of these two apoptosis control strategies

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varies between species and also between cell types, as well as in response to different apoptotic stimuli.

In *C. elegans*, the activation of the ced3 caspase by the ced4 adapter is inhibited by the bcl2-like ced9 protein [2]. The egl1 protein, a BH3 only family protein, is transcribed in cells fated to die [1]. In the presence of egl1, ced9 is inhibited and ced 3 is activated.

In mammalian systems the role of the bcl2 family proteins in regulating caspase activation is more indirect. Upstream signals influence the balance of pro-and anti-apoptotic bcl2 family members, impacting Bax and Bak on the mitochondrial membrane [2]. Bax and Bak induce changes in the mitochondrial membrane, resulting in the release of mitochondrial proteins including Cytochrome-c. Cytochrome-c binds to Apaf-1, forming an apoptosome complex with procaspase-9. Caspase-9 is activated at the apoptosome. Subsequent activation of effector caspases results in cell death.

In flies, a caspase inhibitor, DIAP1, restrains caspase activity in most cells, and cell death is activated when this inhibition is removed [2]. DIAP1 is a member of the Inhibitor of Apoptosis Protein (IAP) family, which can act as direct caspase inhibitors. The RHG proteins, reaper, hid, grim and sickle, bind to DIAP1 and inhibit its anti-apoptotic activity resulting in cell death. The 4 RHG genes are transcribed in various combinations in cells fated to die [3–7]. Interestingly, the process of cell death in flies is very rapid; cells are eliminated within hours of RHG protein expression [3–5]. The bias in the *Drosophila* system towards this more poised apoptotic state may reflect the need for rapid apoptosis activation during development.

IAP proteins can also regulate cell death in mammals. There are 8 IAP family members in humans [8] (see Fig. 1). In the nervous system, there is a role for IAPs in inhibiting caspase activity in apoptosis and in axonal and dendrite pruning [9–11]. SMAC/DIABLO and OMI/HTRA2 are functional homologs of the fly RHG family. These proteins bind to and negatively regulate IAPs and can kill cells under certain conditions [8, 12].

3. Functions of cell death in development

Cell death is prevalent during the development of multicellular organisms. The majority of developmental cell death appears to be apoptotic [13], although alternative death pathways such as autophagy and necrosis may also contribute to the elimination of cells. The amount of cell death occurring during development can be underestimated, as phagocytes often eliminate dying cells within an hour of the initiation of death [14–16].

Examination of the distribution of dying cells and genetic disruption of cell death pathways has revealed important functions of cell death during development. These include the removal of unneeded tissues and cells and amelioration of developmental errors [17]. In certain situations isolated cells die, while in other cases, whole tissues are eliminated.

3.1. Removal of unneeded tissues

Entire tissues can be removed by programmed cell death as part of the initial shaping of the developing organism, or after the tissue has served its function [18, 19]. For example, during

the development of the mammalian reproductive system Mullerian ducts are differentially eliminated from males and Wolffian ducts from females, in response to hormonal signaling [13, 18] The *Drosophila* salivary glands are also removed in response to a steroid hormone pulse after they have served their function [20, 21]. Interestingly, the elimination of the salivary gland requires both apoptotic and autophagic pathways [22–24]. Digit separation in vertebrates involves the elimination of inter-digital mesenchymal cells in response to developmental signaling pathways [25, 26]. Analysis of mutants in the apoptotic machinery suggests that there are backup non-apoptotic pathways that can also contribute to the elimination of these cells [27]. Other examples of tissue elimination during development include the removal of the pronephric kidney in mammals and loss of the tadpole tail and intestine [17].

3.2. Removal of unneeded cells

The death of isolated cells is seen in many developing tissues, but is best described in the developing nervous system. Many more cells are generated during nervous system development than are present in the fully developed tissue. Roughly 10 % of cells in the *C. elegans* nervous system are removed by apoptosis [28, 29]. In *Drosophila* and mammals the number of cells eliminated rises to more than 50% [3, 28–31]. Programmed cell death in the nervous system is likely to play an important role in developmental plasticity. Production of excess cells and their later elimination facilitates the matching of neurons to their targets [32].

The phenotype of cell death mutants illustrates the importance of apoptosis in nervous system development. Deletion of pro-death genes can result in severely malformed nervous systems in mammals and flies. Mice deficient for Caspase-3, caspase-9 and Apaf-1 show persistent neural precursors and exhibit nervous system patterning defects such as multiple indentations of the cerebrum and periventricular masses [33–38]. Interestingly, these phenotypes may not be caused by the survival of large numbers of cells, but rather may be secondary to the inappropriate survival of an FGF8 signaling center, resulting in defects in neural tube closure and insufficient brain ventricle expansion [39].

Bcl-2 family proteins also play a significant role in developmental cell death. Mice null for Bcl-2 family genes show defects in early nervous system development. For example, mice deficient for the anti-apoptotic Bcl-XL and Mcl-1 proteins die early in development due to massive apoptosis of immature neurons and hematopoietic system [40, 41]. Mice null for Bax, a pro-apoptotic member of the Bcl-2 family, have increased numbers of neurons, which are resistant to apoptosis induced by nerve growth factor deprivation [42]. Pro-apoptotic BH3-only proteins have redundant functions in developmental apoptosis. Individual knockouts of Bid, Bim and Puma result in only minor delays in developmental death of neurons. However, simultaneous deletion of all the three genes results in a strong resistance to stress-induced death in cerebellar granule neurons [43].

In the fly, apoptosis also plays an important role in shaping the developing central nervous system. Apoptosis is required to eliminate both dividing progenitors and differentiated neurons in *Drosophila* development [3, 44–47]. For example, neural stem cells are eliminated in the abdominal segments of the developing ventral nerve cord at the end of

embryogenesis [3, 48]. This alters the morphology of the central nervous system to match the transition from a crawling larva to an adult fly. In the absence of apoptosis, the ventral nerve cord is massively expanded [44, 47]. Neural stem cells in the abdominal ventral nerve cord are eliminated in response to developmental pathways including Hox genes and Notch signaling [49]. Interestingly, individual neuronal lineages are also shaped by selective cell death in response to Notch signaling, as described below [50].

Apoptosis is required for the precise organization of the ommatidial units in the developing *Drosophila* eye. Waves of apoptosis sculpt the developing eye, from the earliest specification of photoreceptor and accessory cells to the final tightening of the ommatidial clusters, removing around 2000 excess cells [51]. The regulation of these deaths involve complex interactions between several developmentally important pathways, including the Epithelial Growth Factor Receptor and Notch pathways, as described below [52, 53].

3.3. Developmental correction

Apoptosis can be activated to normalize the developmental defects caused by mutations. This suggests that cell death may also be important for error correction in normal development. For example, in *Drosophila* embryos, misexpression of the bicoid morphogen results in mis-specification of the anterior posterior axis of the fly. Surprisingly, this can be corrected by apoptosis, resulting in a normal animal [54–56]. Mis-expression of the cell cycle regulators *cycE* or *E2F* with *DP* results in a massive increase in cell number due to proliferation. This hypertrophy is also eventually reversed by induced apoptosis, resulting in nearly normal adults [54, 57, 58]. There are numerous other examples where genetic manipulations result in the formation of ectopic cells but the defect is finally corrected by apoptosis [59–62]. Defects caused by the genetic manipulation of *Dpp* and *Wg* signaling is corrected by JNK induced apoptosis in the developing *Drosophila* wing [63]. The role of apoptosis in correcting developmental errors is less well studied in mammals, but increased apoptosis is noted in mis-specified cells in mutant mice [64, 65].

The precise patterning of sensory bristles on the fly thorax provides an elegant example of the role of apoptosis in developmental error correction. During normal development, an excess number of cells become specified as sensory organ precursors. To maintain precise spacing between sensory cells, these aberrant cells are eliminated by Notch induced apoptosis [66].

The examples above provide a glimpse into how apoptosis is an essential aspect of the developmental program. Below we discuss some of the signaling pathways that regulate developmental apoptosis.

4. Regulation of developmental cell death

As described above, the central components of the apoptotic pathway have been extensively characterized. Less is known about how these components are activated in the correct cells at the correct time in development. Many pathways implicated in other developmental processes also regulate developmental cell death (summarized in table 1).

4.1. Notch signaling

Notch signaling is involved in numerous binary cell fate decisions in development, including the life or death decision. In both flies and mammals, Notch is found to bias the choice between survival and death, acting in both directions. Notch influences the survival of neural precursors and differentiating neurons in the mammalian brain. Conditional knockdown of Notch1 and Notch3 in vivo results in increased apoptosis of large number of neural progenitors and differentiating neurons [67]. Notch can also promote apoptosis in the mammalian nervous system. Notch knockouts have been reported to show reduced apoptosis of early neural progenitors [68].

A beautiful example of the two-sided nature of Notch in regulating cell death is provided by the study of hemilineages in the developing *Drosophila* ventral nerve cord. During the postembryonic development of this tissue, neural stem cell divisions can give rise to two distinct hemilineages. In some cases, one of these hemilineages undergoes apoptosis. Notch signaling determines which of these lineages survives [46, 69]. Interestingly, Notch “on” dictates death in 50% of the dying lineages, while Notch “off” promotes death in the remainder. The lack of initiator caspases *Dronc* results in ectopic survival of doomed hemilineages, implying that Notch can regulate the canonical apoptotic pathway to eliminate neuronal lineages [46]. In an elegant recent study of *Drosophila* optic lobe neurons, temporal patterning by specific transcription factors was shown to differentially control Notch dependent death. Interestingly, the upstream regulators of most of the *Drosophila* apoptosis, *rpr* *grim* and *hid* genes in RHG cluster, were found to be differentially responsible for the fate of Notch “on” and Notch “off” lineages. A *hid* specific genetic deletion rescues Notch “off” lineages while a genetic deletion that removes *rpr* and a regulatory region for *grim* rescues Notch “on” lineages. Thus Notch “on” neurons die in a reaper and *grim* dependent manner, while the death of Notch “off” neurons requires *hid* [47, 70].

In other *Drosophila* tissues, Notch has been reported to induce apoptosis. For example during eye development, superfluous inter-ommatidial cells are eliminated in a Notch-dependent manner to maintain the correct spacing between ommatidia [71–73]. Recent studies have demonstrated the Notch target *Su(H)* can directly regulate transcription of the RHG gene *hid* [74]. Given the extensive involvement of Notch in many developmental processes, it is likely that Notch contributes widely to life or death decisions in development.

4.2. RAS/MAPK signaling

Ras signaling is activated downstream of receptor tyrosine kinases, many of which promote cell survival [75]. Ras activates both the Raf/MAPK (ERK) and the PI3K pathways, and is often hyperactivated in tumors. Alongside its well-known role in cancer development, Ras signaling regulates cell death in development. For example, deletion of the Ras/ERK pathway components *Mek1* and *Mek2* in mouse skin results in significant apoptosis in both the embryo and the adult [76]. Deletion of ERK 1 and ERK2 in the developing mouse central nervous system leads to significant apoptosis in a variety of cell types [77].

In the developing *Drosophila* eye, the Epidermal Growth Factor Receptor (EGFR), acting through the Raf/MAPK pathway, provides a precise short-range signal for cell survival [78–81]. Loss of EGFR signaling or ectopic expression of EGFR inhibitor, Argos, results in massive apoptosis in the *Drosophila* eye, while ectopic expression of EGFR signaling results in persistent cell survival and tissue hypertrophy [71, 78, 82, 83]. Loss of RAS and MAPK signaling also results in tissue loss [84, 85]. EGFR/Ras/MAPK signaling suppresses apoptosis in the fly by suppressing both the expression and the activity of the pro-apoptotic RHG gene *hid* [79, 80]. Loss of Ras activity results in increased *hid* transcription [79]. MAPK also negatively regulates *hid* activity through phosphorylation [80]. Similarly, in mammalian systems, ERK may promote survival by phosphorylating glycogen synthase kinase-3 (GSK-3) to desensitize mitochondria to apoptotic permeabilization [86].

In the fly, cross talk between the EGFR pathway and other regulatory pathways has been shown to regulate cell death. The Rb tumor suppressor can regulate cell death acting through the EGFR pathway [87]. Rb inhibits apoptosis by keeping E2F1 dependent apoptosis in check [88]. It was shown recently that miR998 acts downstream of Rb and inhibits dCbl, a negative regulator of EGFR pathway, to suppress cell death in flies [87]. Furthermore, cell death inhibitory interactions between miR998/miR29 RNA and Cbl is conserved in human cells [87]. Crosstalk between the EGFR and Notch signaling pathways can also be important in precisely regulating developmental cell death. In the developing *Drosophila* eye, Notch signaling induces apoptosis in the inter-ommatidial cells whereas EGFR/RAS pathway counteracts this signal [89, 90].

4.3 PI3K signaling

The conserved PI3K kinase pathway is important for the regulation of cell growth, proliferation and survival. PI3K signaling is activated downstream of many growth factor receptors, either by direct receptor binding or downstream of Ras activation (see above) [75]. PI3K signaling can promote cell survival through AKT activation. AKT phosphorylates and inactivates a number of targets, including the pro-apoptotic Bcl2 family member Bad and Caspase 9, and regulates gene expression through the Foxo transcription factor [91]. Knockouts of other PI3K pathway components display pleiotropic phenotypes that are consistent with a role for this pathway in promoting survival during development [92]. Paradoxically, when multiple AKT isoforms are deleted in the mouse, there is increased survival of some cell types during development [93].

In the *Drosophila* brain, the elimination of mushroom body stem cells is regulated by a cross talk between insulin/PI3K signaling and the RHG-mediated apoptotic pathway [94]. Normally, mushroom body stem cells are eliminated around mid pupal life through RHG mediated apoptosis [45, 94]. Reduced insulin/PI3 kinase signaling precedes this death, and inhibition of both RHG activity and PI3K signaling prolongs the survival of these cells.

4.4. Hormone regulation

Nuclear receptor signaling pathways are highly conserved between flies and mammals. In both, flies and vertebrates, the survival or death of many cells or entire tissues is influenced by steroid hormones [95, 96]. Steroid hormones can be either pro- or anti-apoptotic,

mediating the expression of targets such as Bcl2 to inhibit death, or pro-apoptotic Bcl2 family members to activate death.

In *Drosophila*, apoptotic and autophagic pathway components are transcriptionally regulated in response to the steroid hormone ecdysone [23, 97–99]. The pro-apoptotic genes reaper, and hid, the caspases Dronc and Drice, and the adaptor dark are transcriptionally up regulated in response to ecdysone signaling, while the antiapoptotic proteins DIAP1 and DIAP2 are down regulated [98, 100–104]. Recently, it has been shown that the ecdysone receptor complex cooperates with chromatin-modifying cofactors to regulate the transcription of several cell death genes [105–107]#

4.5. Hippo signaling

The Fat/Hippo signaling pathway also regulates cell death. Yorkie (Yki), the most downstream target of the hippo pathway, promotes cell survival in *Drosophila* by negatively regulating the pro-death gene hid and activating pro-survival factors such as bantam and DIAP1 [108]–[109]. Upon activation, hippo signaling exerts its pro-death effect by negatively regulating Yki through phosphorylation. In hippo mutants, retina cells show exuberant proliferation and persistent survival due to inhibition of apoptosis [110–115]. Similarly, the human homologue of Yki, YAP, is elevated in cancer and contributes to cell survival in development and cancer [116–120].

4.6. Hox and Polycomb

Hox genes play a conserved role in controlling anterior-posterior patterning in many species. The regulation of apoptosis is an important element of this patterning in worms, mammals and flies. In mammals, several Hox genes control targets that regulate apoptosis [121]. For example, in the mammalian brain *hoxa1* regulates the pruning of neurons in the hindbrain. When *hoxa1* is deleted, ectopic surviving neurons make functional circuits in the postnatal brain [122]. In *C. elegans*, the Hox gene LIN-39 regulates the survival of VC neurons by suppressing the transcription of the *egl1* pro-apoptotic regulator [123].

Hox gene function in *Drosophila* development has been extensively characterized [124]. Many of the Hox genes regulate apoptosis. The Deformed gene, which is involved in head formation, initiates apoptosis to maintain a boundary between the maxillary and mandibular segments of the head [125]. Similarly, *AbdB*, which regulates the formation of posterior structures, activates apoptosis to generate a precise boundary between abdominal segments A6/A7 and A7/A8 [125]. In both cases, the Hox genes regulate the expression of the proapoptotic reaper gene directly. *AbdB* also regulates the survival and death of neuropeptide-expressing neurons in the embryonic nervous system [126, 127]. The *AbdA* Hox gene regulates neural stem cell death in the *Drosophila* embryonic and post-embryonic nervous system, acting upstream of RHG gene expression [49, 128]. Hox-dependent apoptosis is also required in several neuroblast lineages for the proper elimination of unneeded neurons [129]. Interestingly, Hox proteins can suppress autophagy by repressing the expression of autophagy genes [130]. This suggests that Hox proteins can coordinate death and survival pathways to control developmental cell death.

The Polycomb-group protein (PcG) family of chromatin remodelers play a global role in epigenetic gene silencing. The Hox genes are important targets of PcG activity; PcG keeps the activation of Hox genes in check during normal development. Loss of PcG genes like Polycomb, Sex combs extra, and Enhancer of zeste result in the apoptotic removal of neural stem cells, due to aberrant activation of Hox genes [128]. PcG genes may also have a more direct effect on the expression of cell death genes. ChIP analysis indicates that the RHG gene region is tightly suppressed by the activity of PcG proteins [131]. Interestingly this suppression is regulated temporally to alter the sensitivity of RHG genes to be activated at different developmental stages [131].

4.7. Other developmental pathways

Given the complex and dynamic patterns of apoptosis seen in development, it is clear that additional developmental pathways must influence the core death pathways. These may include intrinsic regulators that dictate the identity of a cell at a specific time and place in development, as well as additional extrinsic signaling pathways such as Wnts and BMPs.

The Wnt/Wingless (Wg) pathway is required to regulate numerous developmental processes including apoptosis [132]. Depending on the cellular context it influences apoptosis positively as well as negatively [133–135]. Activation of Wnt induces apoptosis in hematopoietic progenitor cells [136]. On the other hand, its suppression induces apoptosis in mouse cranial neural crest and Drosophila neurons [137, 138]. On the other hand Wnt/Wg induces RHG mediated apoptosis to precisely remove incomplete ommatidial units at periphery of developing eye in Drosophila [139]. In human disease, Wnt/Wg signaling is implicated in photoreceptor apoptosis in retinal degeneration and neural apoptosis in Alzheimer's disease [140].

The BMP/Dpp family of secreted ligands are members of the TGF-beta super-family. BMP signaling is important for the removal of the interdigital web in mammals [141]. Moreover, BMP signaling is known to regulate apoptosis in the context of forebrain development, where it triggers apoptosis in prospective neural crest cells [142, 143], and during morphogenesis of the chick eye [144]. Ectopic induction of BMP/Dpp signaling can cause apoptosis in isolated mouse neural stem cells [145]. In Drosophila, BMP/Dpp can regulate apoptosis through JNK signaling [63, 146, 147].

Intrinsic temporal and cell identity pathways clearly play a role in regulating cell death in the mammalian and Drosophila nervous system. A recent study demonstrates that cortical interneuron death in mice is independent of external signals. Cultured or transplanted interneurons die at the same time and at the same rate as their counterparts in vivo [148]. Drosophila neural stem fate is autonomously regulated by the temporal series of transcription factors that dictates neural stem cell identity [149]. These transcription factors also decide the fate of neural stem cells by precisely regulating the timing of their death [45].

5. Future directions

Apoptosis is a prevalent cell fate in during development. Pathways that regulate other developmental events can also regulate cell death. It is interesting to note that some regulatory pathways can activate or suppress cell death, depending on the developmental context. The temporal and tissue specific context cues that alter the cell death response will be an interesting area for future research. Until now, these studies have been difficult in vivo, given the rapidity of the apoptotic process from initiation to clearance. New technical advances should facilitate such studies, including new methods for isolating and analyzing gene expression and chromatin changes in small numbers of cells [150–154].

Perturbations in cell death contribute to a variety of human diseases such as cancer and neuro-degeneration. We expect that a greater understanding of the context specific activation of cell death during development could provide insight into how cell death can be accurately manipulated in the treatment of human disease. By examining how developmental pathways intersect with the conserved core apoptotic machinery, we may learn how cancer cells become resistant to cell death or how to prevent cell death in neurodegenerative diseases such as Parkinsonism. In vivo studies are essential to fully appreciate the complexity of cell death regulation.

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Gene abbreviations

AbdA	Abdominal A
AbdB	Abdominal B
apaf-1	Apoptotic protease-activating factor 1
BMP	Bone morphogenetic protein
ced3	cell death protein-3
Ced4	Cell death protein 4
Ced9	cell death protein-9
cycE	Cyclin E
Cyt-c	Cytochrome-c
Dark	Apaf-1 related killer DARK
DIABLO	direct IAP binding protein with low pI
DIAP1	Drosophila inhibitor apoptosis protein 1
DP	Dimerizing partner protein
Dpp	Decapentaplegic

E2F	Transcription factor E2f
EGFR	Epidermal growth factor receptor
Egl1	Egg-laying defective protein 1
ERK 1	extracellular-signal-regulated kinases1
ERK2	extracellular-signal-regulated kinases2
FGF8	fibroblast growth factor 8
Foxo	Forkhead box O
GSK-3	glycogen synthase kinase-3
Hox	Homeobox genes
IAPs	Inhibitor of Apoptosis
JNK	c-Jun N-terminal kinases
LIN-39	abnormal cell LINEage-39
MAPK	mitogen-activated protein kinase 1
Mek1	mitogen-activated protein kinase kinase 1
Mek2	mitogen-activated protein kinase kinase 2
OMI/HTRA2	HtrA serine peptidase 2
PcG	Polycomb-group protein
PI3K	Phosphoinositide 3-kinase
Rb	Retinoblastoma
RHG	Reaper, hid, grim
sce	Sex combs extra
SMAC	Second mitochondria-derived activator of caspase
Su(H)	Suppressor of Hairless
Wg	Wingless
YAP	Yes-associated protein
Yki	Yorkie

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Highlights

- Apoptosis is a common developmental cell fate
- Core apoptotic signaling is highly conserved
- Several developmentally important signaling pathways influence the regulation of apoptosis.
- Pathways regulating developmental cell death may contribute to disease.

Figure 1. Core cell death machinery in *C. elegans*, *Drosophila* and mammals
The core cell death pathway is evolutionarily conserved. Homologues across each row are represented with symbols. Their interactions are shown graphically. Bir1,2 in worms and Cytochrome c in flies have not been shown to play a major role in programmed cell death (gray). Buffy (underlined) can be either pro-[155] or anti- apoptotic [156, 157]. Details of individual genes in the pathway can be found in [17, 26, 158]

Table 1

Signaling pathways that regulate developmental cell death

Gene	Effect on cell death	Model	References
AbdA	Positive	Drosophila	[45, 49, 129]
Deformed	Positive	Drosophila	[125]
AbdB	Positive and negative	Drosophila	[125–127]
hoxa1	Positive	Mammals	[121, 122]
LIN-39	Negative	C. elegans	[123]
PcG proteins (Polycomb, Sex combs extra & Enhancer of zeste)	Negative	Drosophila	[128, 131]
Notch, Notch 1, Notch 3, Su(H)	Positive and negative	Drosophila, Mammals	[46, 49, 50, 52, 53, 66–74, 90]
Ras signaling	Negative	Drosophila	[75, 79, 80, 85]
MAPK/ERK Mek1 and Mek2, signaling	Negative	Drosophila, mammals	[76, 77, 86]
Epidermal Growth Factor Receptor (EGFR)	Negative	Drosophila	[78, 81–84]
Argos	Positive	Drosophila	[83]
Retinoblastoma (Rb)	Negative	Drosophila, mammals	[87, 88]
miR998	Negative	Drosophila	[87]
Cbl	Negative	Drosophila, mammals	[87]
AKT	Positive and negative	Drosophila, mammals	[91–93]
PI3K pathway	Negative	Drosophila, mammals	[75, 91, 92, 94]
Steroid hormone signaling	Positive and negative	Drosophila Mammals	[95–107, 159]
Hippo pathway	Positive	Drosophila mammals	[108–116]
Yorkie/YAP	Negative	Drosophila, mammals	[116–120]
Wnt/Wg pathway	Positive and negative	Drosophila mammals	[132–140]
BMP/Dpp family	Positive	Drosophila, mammals	[140–147]