Review

Implications of *Drosophila* neuroblast development for tumorigenesis

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Abstract

Background: Tumors are characterized by excessive proliferation and the capacity for metastasis. Understanding the detailed mechanisms of tumor progression is crucial for both tumor prevention and targeted therapy. *Drosophila* melanogaster neural stem cells, referred to as neuroblasts (NBs), serve as an ideal model for studying tumorigenesis by recapitulating conserved cellular behaviors, signaling pathways, and regulatory mechanisms. NBs possess self-renewal capacity, enabling them to undergo multiple rounds of proliferative divisions, similar to cancer stem cells. Moreover, several signaling pathways and cytokines that regulate NB development also play a critical role in tumorigenesis. For instance, the absence of key factors in NB development, such as Brat and Numb, can lead to tumor formation. **Objective:** This review focuses on the mechanisms of NB development—including delamination, quiescent NB reactivation, asymmetric cell divisions, and termination—which parallel key tumor processes, such as cell epithelial-mesenchymal transition, stem cell quiescence and reactivation, uncontrolled proliferation, and cell elimination. **Conclusion:** We summarize recent findings on these tumor progression processes. These insights provide valuable clues for understanding tumor progression and offer potential avenues for tumor prevention and treatment.

Keywords: Neuroblasts, Neuroblast delamination, Quiescent neuroblast reactivation, Neuroblast asymmetric cell divisions, Neuroblast termination, Tumorigenesis

1. Introduction

Several characteristics of tumor formation have been elucidated[1] but fully understanding tumors remains a challenge. Epithelial-mesenchymal transition (EMT) can promote tumor migration[2] and drug resistance.[3,4] Tumor cell dormancy is often associated with tumor recurrence and metastasis.[5] Cancer stem cells, which originate from normal stem cells,[6] possess the ability to self-renew and proliferate.[6] In addition, normal cells that fail to exit the cell cycle promptly can also trigger tumor formation.[7] An more in-depth understanding of these processes is essential for tumor prevention and treatment.

Drosophila neural stem cells, known as neuroblasts (NBs), provide an excellent model for studying tumorigenesis due to their larger size, clearer asymmetric cell division pattern, and the involvement of homologous genes.[8,9] NB development and tumorigenesis share several key features. NBs delaminate from the neuroectoderm during the early embryonic stage and then undergo multiple rounds of asymmetric divisions to proliferate.[10] The processes of NB delamination and proliferation resemble tumor metastasis and tumor cell proliferation. During development, NBs enter a quiescent stage in the late embryonic stage and are reactivated approximately 24 h after larval hatching.[10-12] The reactivation of quiescent NBs is analogous to the quiescence and reactivation of tumor stem cells. NBs terminate their proliferation through Prospero (Pros)-dependent cell cycle exit or *reaper*/*hid*/*grim* genes-initiated apoptosis, which is regulated by temporal transcription factors.[13-15] Disruptions in temporal identity or failures of cell cycle exit can lead to cell overgrowth.[16-20]

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Moreover, *Drosophila* has facilitated the initial discovery of the signaling pathways critical in tumor research, such as Notch and Hippo signaling pathways.[21] The Notch name refers to the wing morphology defect.[22] Several signaling pathways and cytokines that regulate NB development also play pivotal roles in tumor formation, progression, and metastasis. For example, the reactivation of *Drosophila* NBs requires the PI3 kinase (PI3K) metabolic pathway,[23] which is also involved in the recurrence of dormant tumor cells in metastatic cancer stem cells.[23,24] In contrast to the tumor-promoting role of the PI3K pathway, the Hippo pathway, which is essential for quiescent NB reactivation, acts as a tumor suppressor.[25,26] The Notch pathway, necessary for NB initiation and proliferation, is also activated in many tumors.[27] Cyclin E promotes the G1 to S transition in embryonic NBs to facilitate the asymmetric division and proliferation of MP2 NBs.[28] Cyclins are highly expressed in breast cancer, pancreatic cancer, endometrial cancer, and head and neck cancer (HNC), where they can serve as prognostic markers.[29,30] Defects in NB development are linked to tumorigenesis. For instance, loss of polarity or spindle dysregulation in NBs is closely associated with tumor-like proliferation.[31-37] The antitumor effects of *Drosophila* asymmetric division have also been demonstrated.[38]

In this paper, we summarize the mechanisms of NB development, including NB delamination, quiescent NB reactivation, NB asymmetric cell divisions, and NB termination and review recent insights into tumorigenesis. These findings provide a foundation for understanding tumor progression and offer potential for tumor prevention and treatment.

2. NBs delamination and tumor EMT

2.1. NBs delamination and EMT

NB origination involves the delamination of selected NB candidates from neuroepithelia, followed by an increase in cell size to form NBs.[39] This process resembles EMT, which refers to the transformation of highly adherent epithelial cells into loosely organized mesenchymal cells.[40] During NB delamination, myosin drives apical contraction and loss of adherens junctions (AJs), leading to cell extrusion in a specific direction.[41-43] Epithelial cadherin (E-cadherin), known as DE-cadherin in *Drosophila*, is a crucial regulator of NB delamination and plays a significant role in EMT.[44] In addition, several signaling pathways involved in NB delamination may also contribute to EMT. For instance, the Notch signaling pathway regulates both NB delamination and proliferation in the ventral neurectoderm.[45,46] Research on *Drosophila* epithelial cells has demonstrated the relationship between the Notch signaling pathway and AJs formation, which has been corroborated in neurodevelopmental studies of spinal animals.[47,48]

The primary driver of EMT is the reduction in cell adhesion and polarity, rendering mesenchymal cells susceptible to delamination from their original tissue.[40] EMT can be triggered by the downregulation of epithelial markers, such as E-cadherin, or the upregulation of mesenchymal markers, such as neuronal cadherin (N-cadherin),[49] which promote NB release from their home sites.[46] Key regulatory factors in EMT include the *Snail*, *Twist*, and Zinc finger e-box-binding homeobox family genes.[50] These factors play a critical part in NB delamination.[46,51] EMT is also closely linked to tumorigenesis. Upregulation of E-cadherin can inhibit tumor progression, particularly by suppressing epithelial tumor invasion and the growth of certain solid cancers.[52-54] However, upregulated E-cadherin or N-cadherin can also facilitate metastasis in breast cancer or invasion in glioma.[55-57]

2.2. NBs delamination and tumor EMT

Studies on cancer cell EMT support the findings from NB delamination research. It has also been demonstrated that the selection and delamination of *Drosophila* NBs are linked to the interplay between EMT and Notch signaling.[58-61] Recent studies have further revealed that the Notch pathway regulates SoxNeuro (*SoxN*) and Worniu (*Wor*) expression by promoting NB stratification (layered separation from neuroepithelium) and EMT. These findings suggest extensive interactions between the Notch pathway, *SoxN*, *Wor*, and EMT.[46] The Notch pathway exhibits context-dependent functions in tumorigenesis.[62-66] Studies on *Drosophila* NBs have confirmed the role of Notch in promoting tumor metastasis.[46,59] The role of *SoxN* in tumors has been extensively investigated. Research on human homologs of *SoxN* (*SOX1* and *SOX2*) has shown that *SOX1* generally exerts an inhibitory effect in most tumors, such as cholangiocarcinoma, nasopharyngeal carcinoma, cervical cancer, and liver cancer.[67-70] However, *SOX1* shows carcinogenic activity in glioblastoma.[71] In contrast to *SOX1*, *SOX2* promotes pulmonary and esophageal squamous cell carcinomas (SCCs).[72] The Snail family genes, including *SNAIL*, *ESCARGOT*, and *WORNIU*, play a part in EMT. *SNAIL* inhibits E-cadherin expression, indicating that it is able to induce EMT.[73] This has been validated in studies on mammary and hypopharyngeal cancer, suggesting *SNAIL* can serve as a potential target for targeted therapy.[73-76]

2.3. The potential mechanisms of NBs delamination and tumor EMT

The regulation of EMT by E-cadherin, Snail, and Notch occurs at the transcriptional or post-transcriptional level. Studies on intercellular connections in *Drosophila* embryonic NBs have shown that myosin II regulates EMT through post-transcriptional mechanisms, promoting the disintegration of AJs and facilitating the entry of NB from the epithelium into

the mesenchyme through apical contraction.[43] Research on ovarian cancer has demonstrated that inhibiting myosin II expression can enhance tumor cell invasion and migration.[77]

3. NBs reactivation and tumor cell initiation

3.1. Extrinsic cues and intrinsic factors in NBs reactivation

Drosophila NBs enter a quiescent state during the late embryonic stage and are reactivated approximately 24 h after larval hatching. Extrinsic factors, including dietary nutrients or nutrient-dependent growth signals, such as P13K and Notch signaling pathways, regulate the reactivation process.[11,12,78,79] In addition, the Hippo signaling pathway is also implicated in this process.[80] The activation of P13K is dependent on *Drosophila* insulin-like peptides (Dilps), particularly Dilp-6 and Dilp-2, which are secreted by nutrition-dependent glial cells.[11,12,78] While P13K activity promotes NB reactivation, the Hippo and Notch signaling pathways inhibit this process. When the Hippo pathway is activated, Hippo or Warts (Wts) kinase inactivates Yorkie (Yki), preventing Yorkie from entering the nucleus.[81,82] This results in a delay in NB reactivation.[80] Conversely, the inactivation of the Notch signal is necessary for NB reactivation under conditions of dietary nutrient availability. After reactivation, NBs activate the Notch pathway, which subsequently promotes cell proliferation. This suggests that the Notch signaling pathway can inhibit NB reactivation.[79]

The reactivation of NBs also requires intrinsic factors. PR-Set7, a histone H4K20 monomethyl transferase,[83] plays a critical role in this process. Studies on *Drosophila* larval brains have shown that the deletion of PR-Set7 reduces cyclin B expression and activates DNA damage checkpoints, indicating that PR-Set7 is essential for maintaining cell cycle progression. NB reactivation is impaired in PR-Set7 mutants.[84,85] Recent research has identified two binding targets of PR-Set7, Earthbound1 (Ebd1) and Cyclin-dependent kinase 1 (Cdk1).[85] Ebd1 is a transcriptional coactivator of the Wingless/Wnt pathway.[86,87] The expression of Ebd1 and Cdk1 is regulated by PR-Set7,[85] suggesting that PR-Set7 promotes NB reactivation by modulating the Wingless/Wnt pathway and the expression of cyclin-dependent kinases.[85]

3.2. Quiescent NBs reactivation and tumor cell initiation

In general, the reactivation of quiescent stem cells facilitates tissue development and regeneration.[88] However, the re-entry of cells into the G0/G2 cell-cycle phase may lead to over-proliferation. Many of the signaling pathways and factors involved in quiescent NB reactivation are also implicated in tumorigenesis or mechanisms of tumor-targeted therapy. For example, the P13K pathway is frequently activated or mutated in many solid cancers and SCCs, including breast cancer, colorectal cancer (CRC), head and neck SCCs (HNSCC), and lung squamous cell carcinoma (LUSC).[89-92] The activation of the Hippo signaling pathway inhibits breast cancer metastasis, liver cancer oncogenesis, and promotes tumor suppressor activity in lung cancer.[93-95] Conversely, the inactivation of Hippo signaling promotes tumor cell proliferation in CRC.[96] *YAP* (homologous gene of *Yki*) was initially identified as an oncogene[97,98] and has been extensively studied in liver cancer, gastric cancer, non-small cell carcinoma (NSCLC), and breast cancer, where it promotes tumor growth and metastasis.[98-101] However, recent studies have shown that *YAP* can act as a tumor suppressor in certain malignancies, such as HNC, CRC, breast cancer, and hematological cancers.[102-105] CDK1 is highly expressed in various tumors, including melanoma, CRC, breast cancer, bladder cancer, lung cancer, HNSCC, and hepatocellular carcinoma (HCC).[106-112] CDK1 promotes tumor cell proliferation and progression through synergistic interactions with other factors.[106-110,112,113] Moreover, the potential role of PR-Set7 in NB proliferation and tumorigenesis has been uncovered.[114,115] Among these findings, the P13K and Hippo signaling pathways have been targeted for the treatment of breast cancer, liver cancer, and other cancers.[116-118] Meanwhile, G2 quiescent cell reactivation and nutritional signaling give us new hints for tumor therapy.[12,119]

4. NB asymmetric division and tumorigenesis

Drosophila NBs are characterized by asymmetric cell divisions. Following each asymmetric division, an NB generates one newborn NB and one ganglion mother cell (GMC; generated in type I NB division) or one intermediate neural progenitor (INP; generated in type II NB division). The newborn NB contributes to division, producing another daughter NB and GMC/INP, a process known as self-renewal.[120] The asymmetric division of NB is regulated by both intrinsic mechanisms and extrinsic factors. Any disruption in asymmetric cell division can lead to tumor formation.

4.1. Intrinsic mechanisms and tumorigenesis

The intrinsic mechanisms underlying NB asymmetric division involve a series of asymmetrically localized cytokines, apical polarity regulation proteins, and cytoskeletal proteins. The asymmetrically localized cytokines dictate cell fate, while apical proteins regulate the orientation of mitotic spindles and the asymmetric segregation of cytokines.[121] Cytoskeletal proteins and related genes control the morphological changes of NBs and the positioning of the cleavage furrow.[122] In addition, several signaling pathways and other factors are involved in the intrinsic regulation of asymmetric division.

The asymmetrically localized fate determinants include Numb, Pros, Brain tumor (Brat), and Staufen (Stau). These

factors localize to the basal side of mitotic NBs during cell division[123-127] and are subsequently segregated into the GMC after mitosis.[123,124] Except for Stau, mutations in any of these factors lead to excessive cell proliferation and promote tumor formation.[33,35,120,127-131] Consequently, Numb, Pros, and Brat are regarded as tumor suppressors.[33,35,127-130] The tumor-suppressive role of TRIM3, the human homolog of Brat, has been confirmed in glioblastoma and brain tumors.[132,133] Numb, an inhibitor of Notch,[134] suppresses tumor-like overgrowth.[135] However, the role of NUMB in tumorigenesis is complex, as studies on NSCLC have shown that certain isoforms (NUMB isoform 2 and NUMB isoform 4) are associated with Notch activation and may promote tumor formation.[136] STAU2, the human homolog of Stau, promotes tumor cell growth and invasion through post-transcriptional regulation and is negatively correlated with prognosis.[137]

Apical proteins form apical protein complexes that include three main groups: the Bazooka (Baz), Par-6, atypical protein kinase C (aPKC) complex; the Insc-Pins, Gαi, Mud complex; the Scribble, Discs large 1, Lethal (2) giant larvae complex. These complexes maintain NB apical polarity, coordinate mitotic spindle orientation, and regulate the segregation of basal proteins.[31,34,138-145] These proteins are also implicated in tumorigenesis. Baz and Par-6 exhibit tumor-suppressive functions. PARD3, the human homolog of Baz, inhibits tumor cell proliferation, invasion, and EMT in esophageal SCC.[146] The tumor-suppressive role of *PARD6G* (a *Par-6* homolog) has been further demonstrated in human cancers, particularly epithelial cancers, where *PARD6G* is frequently absent in tumors, such as breast, lung, and ovarian cancers.[147] PRKCI, the human homolog of aPKC, is highly expressed in many tumors[148,149] and can act synergistically with other oncogenic factors to promote tumorigenesis.[35,150] In most tumors, the expression of INSC is reduced.[151] In breast cancer, INSC forms tetramers with the LGN (a Pins homolog), inhibiting symmetric division and the proliferation of cancer stem cells.[152] In NBs, the mushroom body defect (Mud) binds to Pins and coordinates the mitotic spindle with the polar axis. Mud deficiency leads to symmetric division, mimicking tumor cell proliferation, suggesting that Mud may suppress tumorigenesis.[31,34] However, CENPF, the homolog of Mud, promotes tumor progression in breast cancer, papillary thyroid cancer, cervical cancer, adrenocortical carcinoma, liver cancer, and lung adenocarcinoma (LUAD), and is associated with unfavorable prognosis.[153-157] The role of LGN varies across different tumors. In NSCLC, the expression of *GPSM2* (a *Pins* homolog) is positively correlated with prognosis, and LGN inhibits EMT and tumor cell metastasis.[158] In contrast, in liver cancer and pancreatic adenocarcinoma, *GPSM2* is negatively associated with prognosis.[159,160] The Scribble polarity module has tumor-suppressive effects in various cancers, including breast, prostate, lung, and skin cancers.[161-168]

Prefoldin promotes the production and normal function of cytoskeletal proteins during asymmetric cell division.[169,170] Two subunits of Prefoldin, merry-go-round and Prefoldin2 (Pfdn2), regulate asymmetric cell division and inhibit the ectopic formation of NBs. The inhibitory effect of Pfdn2 on NB overgrowth is partially mediated by its interaction with Pins.[170] Prefoldins (PFDNs) are highly expressed in a multitude of cancers[171] and promote tumor metastasis by activating the cytoskeleton, inhibiting cyclins, and activating tumor-related signaling pathways.[172-174] PFND2, the human homolog of Pfdn2, is associated with poor prognosis in tumors, such as HCC, gastric cancer, and metastatic urothelial carcinoma.[137,175,176] Studies on PFND1, the human homolog of Prefoldin1 (Pfdn1), in gastric cancer, HCC, and pulmonary cancer indicate that PFND1 promotes tumor metastasis[173,174] and its expression level was negatively correlated with prognosis.[137,174]

In addition to these factors, a number of signaling pathways involved in asymmetric division also play roles in tumorigenesis. The Notch signaling pathway is central to NB asymmetric division and daughter cell fate determination. Before asymmetric division, Notch signaling ensures the asymmetric localization of Numb, which determines the fate of the daughter cells.[135] After division, Notch signaling is antagonized by Numb in GMCs, preventing dedifferentiation into NBs.[177-179] Notch signaling also serves a dual role in tumorigenesis, inhibiting epidermal carcinomas, such as cutaneous cancers and LUSC[180-182] while promoting solid cancers, such as breast cancer.[65] The Rap1-Rgl-Ral signaling pathway regulates NB polarity and spindle orientation. Mutations in Rap1 GTPase lead to symmetric cell division.[183] RAP1A, the human homolog of Rap1, promotes tumor metastasis by activating various signaling pathways.[184] The Hippo signaling pathway is also involved in asymmetric division. Wts, which interacts with Cno, Rap1, aPKC, Baz, Insc, Pins, and Gαi, is essential for the asymmetric localization of apical proteins and cytokines.[185] Wts is a tumor suppressor.[186] Its homolog, LATS1, inhibits the proliferation and metastasis of CRC cells.[187]

4.2. Extrinsic factors and tumor formation

The neuroectoderm may regulate cell polarity and cell division by secreting signaling substances. *Drosophila* cortex glial cells secrete Netrins and Slit (Sli), which regulate the asymmetric division of larval NBs through the Fra and Robo1 or Rac1-Cdc42 signals, respectively. Disruption of either the Netrin-Fra or Sli-Robo1 pathway leads to ectopic NB proliferation.[121] Sli has been shown to inhibit tumor cell proliferation and migration.[188-190] Netrins are associated with thoracic aortic aneurysm cytoskeleton degradation.[191]

5. NBs termination and tumorigenesis

At the late stage of the NB development, NBs exit the cell cycles or undergo apoptosis, terminating their proliferation.[14,192] This process is regulated by temporal patterning and cell cycle factors. Failure in NB termination can lead to prolonged NB proliferation, posing a potential risk for tumor formation.

5.1. Regulation of NB termination

Temporal transcription factors regulate NB termination.[193-195] Embryonic NBs sequentially express Hunchback, Kruppel (Kr), Pdm1/Pdm2, Castor (Cas), and Grainyhead (Grh). These factors exhibit a feedforward activation relationship.[194-199] This sequence of transcription factors is referred to as temporal patterning.[193,194,200] In larval NBs, the temporal patterning differs slightly from that of embryonic NBs. While some factors, such as Cas and Grh, persist, new factors, such as chronologically inappropriate morphogenesis (Chinmo) and broad complex (Br-C), are introduced and sequentially expressed.[14,201,202] Interactions between these factors include the positive regulation of Chinmo by Cas and the negative regulation of Br-C by seven up (Svp).[14] Svp promotes timely cell cycle exit by triggering nuclear Pros accumulation in NBs during the pupal stage.[14,203] In addition, INPs produced by type II NBs exhibit their own temporal patterning with five main factors identified: Osa, Hamlet (Ham), Dichaete (D), Grh, and Eyeless (Ey).[20,204] These factors are sequentially expressed from newly-formed to older INPs.[20,204]

5.2. Tumorigenic role of temporal transcription factors

The roles of these temporal transcription factors in tumorigenesis have been extensively studied. BCL6, the human homolog of Kr, is an oncoprotein[205] well-documented in lymphoma.[206-208] It is also highly expressed in breast cancer, leukemia, and lung cancer, where it sustains tumor cell proliferation.[209-215] BCL6 has been targeted in tumor therapies.[216-218] POU2F3, the human homolog of Pdm2, is expressed in a subset of small cell lung cancer (SCLC).[219] Mouse studies have shown that POU2F3 inhibits tumor metastasis.[220] CASZ1, the human homolog of Cas, suppresses neuroblastoma and rhabdomyosarcoma (RMS).[221,222] However, CASZ1 promotes EMT in epithelial ovarian cancer (EOC).[223] Similarly, GRHL1, the human homolog of Grh, promotes the proliferation of colon cancer cells.[224] In NSCLC, GRHL1 enhances tumor cell proliferation by upregulating cell cycle-related genes and preventing normal cell cycle exit.[225] Conversely, GRHL1 expression is negatively correlated with prognosis in certain tumors, such as esophageal SCC.[226]

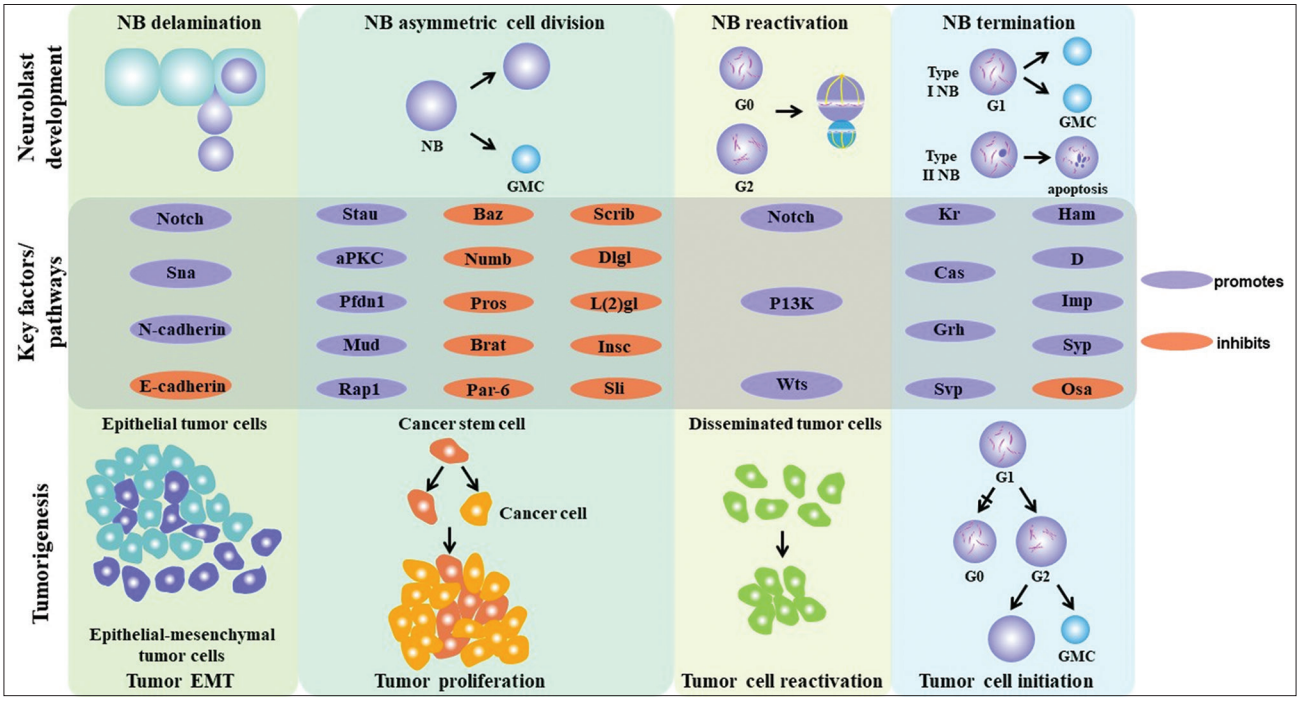

Figure 1. Key factors in *Drosophila* NB development and tumorigenesis. NB development is characterized by distinct stages, including delamination, proliferation through asymmetric division, quiescence and reactivation, and termination. Most factors regulating *Drosophila* NB development also impact tumorigenesis and progression, contributing to processes such as tumor cell EMT, proliferation, initiation, and disseminated cell reactivation. Studies on the roles of these factors in NB development provide insights into their functions in tumorigenesis. Specific factors, including Sna, PI3K, and Cdk1, act as oncogenic drivers. Conversely, Hpo, Wts, Baz, and Brat function as tumor suppressors. In addition, several molecules, such as Notch, E-cadherin, and Syp, exhibit context-dependent roles in these processes.
Abbreviations: EMT: Epithelial-mesenchymal transition; GMC: Ganglion mother cell; NBs: Neuroblasts.

Table 1. Key factors/pathways involved in *Drosophila* neuroblast development and tumorigenesis

Genes name		Main function		Homologous genes	References
		NB	Tumor		
NB delamination	*Shotgun* (*Shg*)	NB delamination	Promotes tumor invasion, metastasis, or prevents progression	*CDH3; CDH2; CDH4; CDH15; L1CAM*	44,52-55,57
	Snail (*Sna*)/ *Worniu* (*Wor*)	NB cell fate initiation and NB cell marker	Promotes tumor invasion and metastasis	Hsap/*SNAI2, SNAI1, SNAI3;* Mmus/ *Snai1, Snai2, Snai3;* Xtro/*snai1;* Atha/ *NTT, WIP4, WIP5;* Drer/*snai1a*	51,73-76,279
	SoxNeuro (*SoxN*)	Proneural gene	Promotes or inhibits tumor	Hsap/*SOX1, SOX2;* Mmus/*So×2;* Xtro/ *so×1, so×2;* Drer/*so×1a, so×1b, so×2*	67-72,280
Quiescent NB reactivation	*Notch* (*N*)	Regulates NB asymmetric division, quiescence, and reactivation	Promotes or inhibits tumor progression, promotes tumor metastasis	Hsap/*NOTCH1;* Mmus/*Notch1, Notch2;* Xtro/*notch1;* Drer/*notch1a;* Cele/*lin-12*	59,79,134,180-182
Quiescent NB reactivation	*Dp110*	Promotes NB reactivation	Promotes tumor	Hsap/*PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R1, PIK3R2, PIK3R3*	11,12,89-92
	Hippo (*Hpo*)	Inhibits NB reactivation	Inhibits tumor	Hsap/*STK3;* Mmus/*Stk3;* Xtro/*stk3, stk4;* Drer/*stk3;* Cele/*cst-1, cst-2;* Atha/*STK1*	80,93-96
	Warts (*Wts*)	Regulates NB asymmetric division and inhibits reactivation	Inhibits tumor	Hsap/*LATS1;* Mmus/*Lats1;* Xtro/*lats2;* Drer/*lats1;* Cele/*wts-1*	80,185,187
	Yorkie (*Yki*)	Promotes NB proliferation and reactivation	Promotes or inhibits tumor	Hsap/*YAP1;* Mmus/*Yap1;* Xtro/*wwtr1, yap1;* Drer/*yap1;* Cele/*yap-1*	80,97-105
	PR-Set7/ SET domain containing 8 (*Set7*)	Maintains cell cycle and promotes NB reactivation	Promotes tumor	Hsap/*KMT5A;* Mmus/*Kmt5a;* Xtro/*kmt5a;* Drer/*kmt5aa;* Cele/*set-1*	84,85,114,115
Quiescent NB reactivation	*Earthbound 1*(*Ebd1*)	Promotes Wingless/Wnt pathway and NB reactivation	-	*No records found*	85,87
	Cyclin-dependent kinase 1 (*Cdk1*)	Promotes NB reactivation	Promotes tumor	Hsap/*CDK1;* Mmus/*Cdk1;* Xtro/*cdk1;* Drer/*cdk1;* Cele/*cdk-1;*	85,106-113
NB asymmetric cell division	*Numb*	Cell fate determinant regulates NB asymmetric division and self-renewal	Inhibits tumor	Hsap/*NUMBL;* Mmus/*Numb;* Xtro/*numb;* Drer/*numbl;* Cele/*num-1*	33,35,134,281
	Prospero (*Pros*)	Cell fate determinant, regulates NB asymmetric division and suppresses self-renewal	Inhibits tumor	Hsap/*PROX1;* Mmus/*Pro×1;* Xtro/*pro×1;* Drer/*pro×1a;* Cele/*pros-1*	127,129,130,282
	Brain tumor (*Brat*)	Cell fate determinant regulates NB asymmetric division and suppresses self-renewal	Inhibits tumor	Hsap/*TRIM3;* Mmus/*Trim3;* Xtro/*trim2;* Drer/*trim2a;* Cele/*ncl-1*	127-130
	Staufen (*Stau*)	Regulates NB asymmetric division	Promotes tumor	Hsap/*STAU2;* Mmus/*Stau1, Stau2;* Xtro/ *stau2;* Drer/*stau1, stau2;* Cele/*stau-1*	126,283
NB asymmetric cell division	*Bazooka* (*Baz*)	Regulates NB asymmetric division and spindle orientation	Inhibits tumor	Hsap/*PARD3;* Mmus/*Pard3;* Xtro/*pard3b, pard3;* Drer/*pard3bb;* Cele/*par-3*	140,141,146
	Par-6	Regulates NB asymmetric division and polarity	Inhibits tumor	Hsap/*PARD6G;* Mmus/*Pard6g;* Xtro/ *pard6g;* Drer/*pard6gb;* Cele/*par-6*	143,147
	aPKC	NB proliferation factor regulates NB asymmetric division	Promotes tumorigenesis	Hsap/*PRKCI;* Mmus/*Prkci;* Xtro/*prkci;* Drer/*prkci;* Cele/*pkc-3;*	35,130,148-150,284,285
	Inscuteable (*Insc*)	Proneural gene regulates NB asymmetric division and spindle orientation	Inhibits tumor	Hsap/*INSC;* Mmus/*Insc;* Xtro/*insc;* Drer/ *insc;* Cele/*insc-1*	122,139,141,151,152
	Partner of inscuteable (*Pins*)	Regulates NB asymmetric division and spindle orientation	Promotes or inhibits tumor	Hsap/*GPSM2;* Mmus/*Gpsm2;* Xtro/ *gpsm2;* Drer/*gpsm2;* Cele/*ags-3*	34,158-160,286,287

(*Cont'd...*)

Table 1. (*Continued*)

Genes name		Main function		Homologous genes	References
		NB	Tumor		
NB asymmetric division	*Mushroom body defect* (*Mud*)	Regulates NB asymmetric division and spindle orientation	Promotes tumor	Hsap/*CENPF, FILIP1;* Mmus/*Cenpf, Krt17;* Xtro/*filip1;* Drer/*filip1b, znf185*	31,34,153-157,288,289
	Scribble (*Scrib*)	Regulates NB asymmetric division	Inhibits tumor	Hsap/*SCRIB;* Mmus/*Scrib;* Xtro/*lrrc1;* Drer/*scrib;* Cele/*let-413*	144,164-166
	Discs large 1 (*Dlg1*)	Regulates NB asymmetric division	Inhibits tumor	Hsap/*DLG1;* Mmus/*Dlg1;* Xtro/*dlg1;* Drer/*dlg1, dlg1l, dlg3;* Cele/*dlg-1*	138,144,161
	Lethal (*2*) *giant larvae* (*L^2*) *gl*)	Regulates NB asymmetric division	Inhibits tumor	Hsap/*LLGL1;* Mmus/*Llgl1;* Xtro/*llgl1;* Drer/*llgl1;* Cele/*lgl-1*	142,144,162,163
	Prefoldin 1 (*Pfdn1*)	Regulates NB asymmetric division	Promotes tumor	Hsap/*PFDN1;* Mmus/*Pfdn1;* Xtro/*pfdn1;* Drer/*pfdn1;* Cele/*pfd-1*	137,169,170,173,174
	Rap1	Regulates the polarity and spindle orientation of NB	Promotes tumor progression	Hsap/*RAP1A;* Mmus/*Rap1a;* Xtro/*rap1b;* Drer/*rap1aa;* Cele/*rap-1*	183,184
NB asymmetric division	*Rgl*	Regulates the polarity and spindle orientation of NB	-	Hsap/*RGL1;* Mmus/*Rgl1;* Xtro/*ralgds;* Drer/*rgl1;* Cele/*rgl-1*	183
	Warts (*Wts*)	Regulates NB asymmetric division	Inhibits tumor	Hsap/*LATS1;* Mmus/*Lats1;* Xtro/*lats2;* Drer/*lats1;* Cele/*Wts-1*	185-187
	Netrin-A (*NetA*)	Regulates NB asymmetric division and proliferation	Increases TAA expression	Hsap/*NTN1;* Mmus/*Ntn1;* Xtro/*ntn1, ntn3;* Drer/*ntn1b;* Cele/*unc-6*	121,191
	Slit (*Sli*)	Regulates NB asymmetric division and proliferation	Inhibits tumor	Hsap/*SLIT3;* Mmus/*Slit3;* Xtro/*slit1;* Drer/*slit3;* Cele/*slt-1*	121,188,189
NB termination	*Hunchback* (*Hb*)	Embryonic temporal transcription factor of Type I NB	-	Hsap/*IKZF5;* Mmus/*Ikzf5;* Xtro/*ikzf5;* Drer/*ikzf5, plagl2, plagx, rest;* Cele/*hbl-1*	194,196
NB termination	*Kruppel* (*Kr*)	Embryonic temporal transcription factor of Type I NB	Promotes tumor	Hsap/*BCL6;* Mmus/*Bcl6;* Xtro/*bcl6;* Drer/*bcl6aa, bcl6ab;* Cele-*B0310.2/lsl-1, ztf-6*	194,196,205,206,209-215
	Pdm2	Embryonic temporal transcription factor of Type I NB	Inhibits tumor	Hsap/*POU2F3;* Mmus/*Pou2f3;* Xtro/*pou2f3;* Drer/*pou2f3;* Cele/*ceh-18*	194,198,219,220
	Castor (*Cas*)	Embryonic temporal transcription factor of Type I NB	Inhibits tumor	Hsap/*CASZ1;* Mmus/*Casz1;* Xtro/*casz1;* Drer/*casz1;* Cele/*lect-2*	194,197,221-223
	Grainy head (*Grh*)	Embryonic temporal transcription factor of NB; regulates NB proliferation	Inhibits or promotes tumor	Hsap/*GRHL1;* Mmus/*Grhl1;* Xtro/*grhl2, grhl3;* Drer/*grhl1, grhl2b;* Cele/*grh-1*	193,199,204,224-226
	Seven up (*Svp*)	Regulates temporal transcription factor expression and timely cell cycle exit	Inhibits or promotes tumor	Hsap/*NR2F2;* Mmus/*Nr2f2;* Xtro/*nr2f1, nr2f2;* Drer/*nr2f1a;* Cele/*unc-55*	14,227-230,290
NB termination	*Chinmo*	Larval transcription factor of NB	-	Hsap/*BTBD18;* Mmus/*Bach2, Btbd18;* Xtro/*btbd18;* Drer/*bcl6aa;* Cele/*R09A1.2*	14,202
	Broad (*Br*)	Larval transcription factor of NB	-	Hsap/*BTBD18;* Mmus/*Btbd18;* Xtro/*btbd18;* Drer/*btbd18;* Cele/*R09A1.2*	14
	Osa	Transcription factor of Type II NB	Inhibits tumor	Hsap/*ARIDA, ARID1B;* Mmus/*Arid1a, Arid1b;* Xtro/*arid1a;* Drer/*arid1b;* Cele/*let-526*	20,236,291
	Hamlet (*Ham*)	Transcription factor of Type II NB; regulates timely cell cycle exit	Inhibits or promotes tumor	Hsap/*MECOM;* Mmus/*Mecom, Prdm16;* Xtro/*mecom;* Drer/*Prdm16;* Cele/*egl-43*	20,231-235
	Dichaete (*D*)	Transcription factor of Type II NB regulates timely cell cycle exit	Promotes tumor	Hsap/*SOX12*	204,237-243
NB termination	*Eyeless* (*Ey*)	Transcription factor of Type II NB	Inhibits or promotes tumor	Hsap/*PAX6*	204,244-253
	Imp	Regulates temporal transcription factor expression and timely cell cycle exit	Inhibits tumor	Hsap/*IGF2BP1, IGF2BP2, IGF2BP3;* Mmus/*Igf2bp1, Igf2bp2;* Xtro/*igf2bp3;* Drer/*igf2bp1, igf2bp2a, igf2bp3;* Cele/*imph-1*	256,262,265-267
	Syncrip (*Syp*)	Regulates temporal transcription factor expression and timely cell cycle exit	Inhibits or promotes tumor	Hsap/*HNRNPR, SYNCRIP;* Mmus/*Hnrnpr, Syncrip;* Xtro/*hnrnpr;* Drer/*syncripl;* Cele/*hrp-2*	262,268,269

Abbreviations: Atha: *Arabidopsis thaliana*; Cele: *Caenorhabditis elegans*; Drer: *Danio rerio*; Hsap: *Homo sapiens*; Mmus: *Mus musculus*; NB: Neuroblast; TAA: Thoracic aortic aneurysm Xtro: *Xenopus tropicalis*.

The role of NR2F2, a homolog of Svp, in breast cancer has been extensively studied. NR2F2 is highly expressed in estrogen receptor (ERα)-positive breast cancer cells,[227] which also express high levels of E-cadherin.[228] Loss of E-cadherin can promote breast cancer growth,[54] suggesting that NR2F2 may possess a tumor-suppressive effect. This is supported by studies showing that NR2F2 inhibits transforming growth factor-β-induced EMT and suppresses tumor cell migration and invasion.[229] However, NR2F2 can also inhibit E-cadherin expression and promote N-cadherin expression in breast cancer, facilitating insulin-induced EMT and enhancing tumor cell migration and invasion.[230] Ham, a transcription factor of Osa, inhibits the generation of additional type II NBs.[20] MECOM, the human homolog of Ham, is highly expressed in leukemia, EOC, and glioblastoma multiforme, with its expression level being negatively correlated with prognosis.[231-234] In LUAD, low MECOM expression may be associated with poor prognosis.[235] ARID1, the human homolog of Osa, suppresses NSCLC. *ARID1* mutations are prevalent and associated with poor prognosis. In HCC and SCC, ARID1 deficiency promotes tumorigenesis and tumor cell proliferation.[236] SOX12, the human homolog of D, promotes tumor cell proliferation and metastasis in CRC, breast cancer, thyroid cancer, multiple myeloma, and HCC.[237-241] High SOX12 expression in tumors is often associated with an unfavorable prognosis.[239,242,243] However, the functions of these temporal factors in tumorigenesis are context-dependent and warrant further investigations.

In retinoblastomas, breast cancer, brain cancer, pancreatic cancer, and CRC, *PAX6*, the human homolog of *Ey*, is highly expressed.[244-247] *PAX6* promotes the progression of breast cancer, pancreatic cancer, and CRC.[246-248] In NSCLC, *PAX6* is upregulated and associated with poor prognosis.[249,250] However, in prostate cancer and glioblastoma, *PAX6* exhibits antitumor effects and inhibits tumor growth.[251-253] These findings suggest that the timing or stage-specific cues may be critical in dictating the role of these genes in tumorigenesis. For example, loss of the early temporal factor *Svp* prevents NB termination, allowing NBs to persist into the adult stage. This may help explain why tumorigenesis occurs in children's brains.[254,255]

5.3. Additional regulatory mechanisms

Additional regulatory mechanisms include post-transcriptional RNA-binding proteins,[256] Hedgehog (Hh) signaling, and the Ecdysone pathway, which are involved in temporal regulation.[257-260] Two RNA-binding proteins, insulin growth factor-II mRNA-binding protein (Imp) and Syncrip (Syp), exhibit an antagonistic role in larval NBs.[256,261-263] Their concentration gradients are inversely correlated over time, with Imp highly expressed in early larval NBs and Syp in late larval NBs.[14,262,264] Imp promotes NB self-renewal and inhibits timely termination, while Syp inhibits self-renewal and promotes NB differentiation.

Overexpression of Imp and knockdown of Syp may promote tumor growth, imparting a hierarchical nature to tumor cell division.[255,256] IGF2BP1, the human homolog of Imp, promotes tumor proliferation by enhancing cell cycle progression and metastasis through the promotion of EMT.[265] IGF2BP1 has been extensively studied in neuroendocrine neoplasms, EOC, and HCC.[265-267] HnRNPK, the human homolog of Syp, plays a significant role in promoting tumorigenesis in liver cancer, gastric cancer, colon adenocarcinoma, and rectum adenocarcinoma.[268,269] However, in colorectal adenocarcinoma, HnRNPK expression is positively correlated with prognosis.[269]

The Hh signaling pathway is frequently activated in several types of tumors, such as medulloblastoma, RMS, basal cell carcinoma, SCLC, stomach cancer, CRC, pancreatic cancer, ovarian cancer, breast cancer, prostate cancer, and hematological tumors. The pathway promotes tumor formation and progression, thus serving as a therapeutic target.[270-277] In brain tumors, the Ecdysone pathway inhibits tumor cell growth, which may be linked to the role of steroid hormones in humans, as suggested by findings in *Drosophila*.[227,278]

6. Conclusion

Drosophila NBs serve as an ideal model for uncovering the mechanisms underlying tumorigenesis. The development of NBs and tumorigenesis shares several key characteristics, including cell delamination/EMT, quiescent cell reactivation, stem cell asymmetric division, and progenitor termination, all of which have been discussed in this review. The genes and signaling pathways involved in these processes are highly conserved (Table 1). Mutations in these factors lead to NB overgrowth in *Drosophila*, while defects in their homologs contribute to tumor initiation (Figure 1). Studies on the mechanisms of NB development have provided valuable insights into tumor formation and progression.

Furthermore, the functions of certain genes in tumors are context-dependent. For instance, the Notch signaling pathway, as well as other factors, such as *CASZ1* (human homolog of *Cas*), *GRHL1* (human homolog of *Grh*), and *NR2F2* (the homolog of *Svp*), can either promote or inhibit tumor growth depending on the context. This duality is complex and requires further investigation. Insights from NB studies may offer detailed explanations. For example, the tumorigenic effects of Svp or Cas deficiencies may be closely linked to the developmental stage (or aging in humans).

Meanwhile, further studies in mammalian cells or humans are needed to determine whether the initiation of certain

cancers is directly linked to these findings in *Drosophila*. For example, although homologs of temporal series genes, such as *BCL6* (the human homolog of *Kr*), *CASZ1* (the human homolog of *Cas*), *GRHL1* (the human homolog of *Grh*), and *NR2F2* (a homolog of *Svp*), as well as steroid hormones, have been implicated in tumorigenesis, it remains unclear whether the tumor cells originate from precursor cells with dysfunctional temporal series gene expression.

In summary, the mechanisms of tumor formation are multifaceted. The applications of *Drosophila* NB development studies to tumorigenesis have significantly advanced our understanding of tumors. This review also provides potential clues for identifying new targets for tumor prevention and treatment in the future.

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Conflict of interest

The authors declare no conflicts of interest.

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