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]

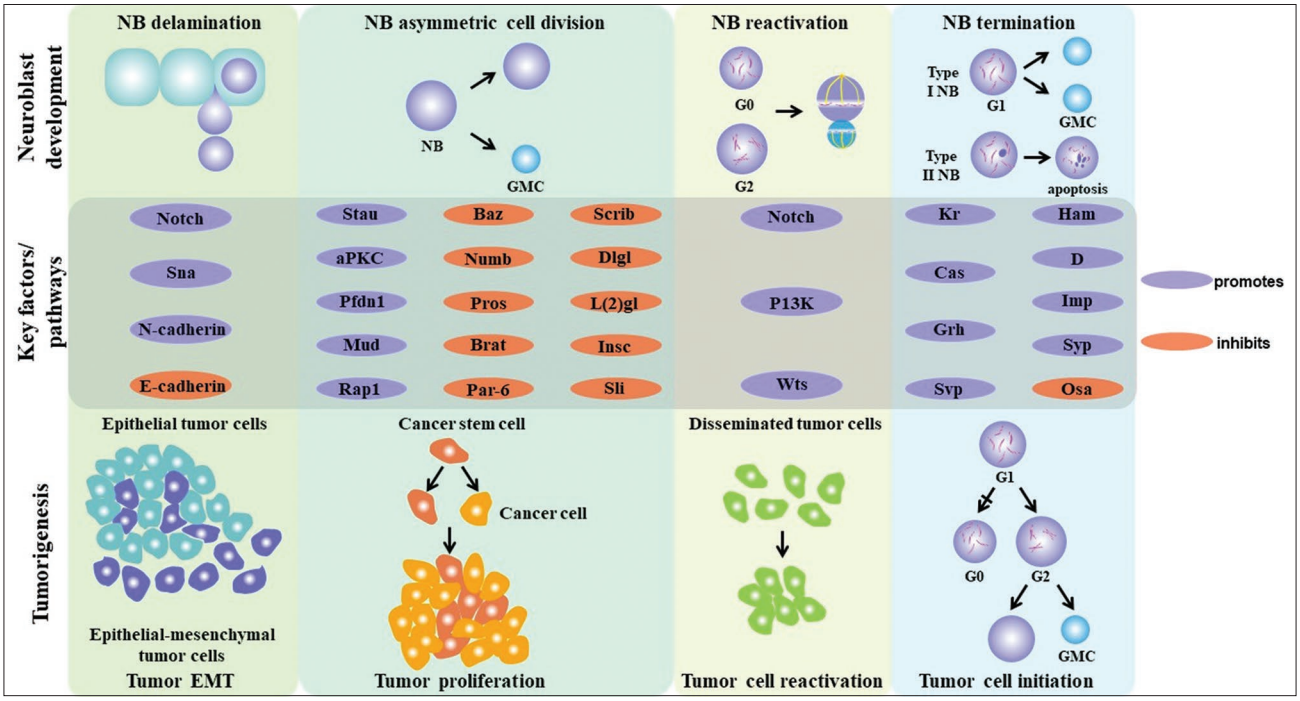

Figure 1. Key factors in *Drosophila* NB development and tumorigenesis. NB development is characterized by distinct stages, including delamination, proliferation through asymmetric division, quiescence and reactivation, and termination. Most factors regulating *Drosophila* NB development also impact 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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References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. *Cell*. 2011;144(5):646-674. doi: 10.1016/j.cell.2011.02.013
2. Nieto MA, Huang RY, Jackson RA, Thiery JP. Emt: 2016. *Cell*. 2016;166(1):21-45. doi: 10.1016/j.cell.2016.06.028
3. Dongre A, Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. *Nat Rev Mol Cell Biol*. 2019;20(2):69-84. doi: 10.1038/s41580-018-0080-4
4. Brabletz S, Schuhwerk H, Brabletz T, Stemmler MP. Dynamic EMT: A multi-tool for tumor progression. *EMBO J.* 2021;40(18):e108647. doi: 10.15252/embj.2021108647
5. Yadav AS, Pandey PR, Butti R, *et al*. The biology and therapeutic implications of tumor dormancy and reactivation. *Front Oncol*. 2018;8:72. doi: 10.3389/fonc.2018.00072
6. Clarke MF, Fuller M. Stem cells and cancer: Two faces of eve. *Cell*. 2006;124(6):1111-1115. doi: 10.1016/j.cell.2006.03.011
7. Sherr CJ. Cancer cell cycles. *Science*. 1996;274(5293): 1672-1677. doi: 10.1126/science.274.5293.1672
8. Doe CQ, Technau GM. Identification and cell lineage of individual neural precursors in the *Drosophila* CNS. *Trends Neurosci*. 1993;16(12):510-514. doi: 10.1016/0166-2236(93)90195-r
9. Bossing T, Technau GM. The fate of the CNS midline progenitors in *Drosophila* as revealed by a new method for single cell labelling. *Development.* 1994;120(7):1895-1906. doi: 10.1242/dev.120.7.1895
10. Kang KH, Reichert H. Control of neural stem cell self-renewal and differentiation in *Drosophila*. *Cell Tissue Res*. 2015;359(1): 33-45. doi: 10.1007/s00441-014-1914-9
11. Sousa-Nunes R, Yee LL, Gould AP. Fat cells reactivate quiescent neuroblasts via TOR and glial insulin relays in *Drosophila*. *Nature*. 2011;471(7339):508-512. doi: 10.1038/nature09867
12. Chell JM, Brand AH. Nutrition-responsive glia control exit of neural stem cells from quiescence. *Cell*. 2010;143(7): 1161-1173. doi: 10.1016/j.cell.2010.12.007
13. Choksi SP, Southall TD, Bossing T, *et al*. Prospero acts as a binary switch between self-renewal and differentiation in *Drosophila* neural stem cells. *Dev Cell.* 2006;11(6):775-789. doi: 10.1016/j.devcel.2006.09.015
14. Maurange C, Cheng L, Gould AP. Temporal transcription factors and their targets schedule the end of neural proliferation in *Drosophila*. *Cell*. 2008;133(5):891-902. doi: 10.1016/j.cell.2008.03.034
15. An H, Yu Y, Ren X, *et al*. Pipsqueak family genes dan/danr antagonize nuclear Pros to prevent neural stem cell aging in *Drosophila* larval brains. *Front Mol Neurosci*. 2023;16:1160222. doi: 10.3389/fnmol.2023.1160222
16. Crompton NE, Saydan N. Control of the cell cycle. *J Neurooncol*. 1994;22(3):255-259. doi: 10.1007/bf01052930
17. Hinds PW, Dowdy SF, Eaton EN, *et al*. Function of a human

cyclin gene as an oncogene. *Proc Natl Acad Sci U S A.* 1994;91(2):709-713.
doi: 10.1073/pnas.91.2.709

18. Tessema M, Lehmann U, Kreipe H. Cell cycle and no end. *Virchows Arch.* 2004;444(4):313-323.
doi: 10.1007/s00428-003-0971-3
19. Zeng X, Lin X, Hou SX. The Osa-containing SWI/SNF chromatin-remodeling complex regulates stem cell commitment in the adult *Drosophila* intestine. *Development.* 2013;140(17):3532-3540.
doi: 10.1242/dev.096891
20. Eroglu E, Burkard TR, Jiang Y, *et al*. SWI/SNF complex prevents lineage reversion and induces temporal patterning in neural stem cells. *Cell.* 2014;156(6):1259-1273.
doi: 10.1016/j.cell.2014.01.053
21. Dey A, Varelas X, Guan KL. Targeting the Hippo pathway in cancer, fibrosis, wound healing and regenerative medicine. *Nat Rev Drug Discov.* 2020;19(7):480-494.
doi: 10.1038/s41573-020-0070-z
22. Siebel C, Lendahl U. Notch signaling in development, tissue homeostasis, and disease. *Physiol Rev.* 2017;97(4):1235-1294.
doi: 10.1152/physrev.00005.2017
23. Fox DB, Garcia NMG, McKinney BJ, *et al*. NRF2 activation promotes the recurrence of dormant tumour cells through regulation of redox and nucleotide metabolism. *Nat Metab.* 2020;2(4):318-334.
doi: 10.1038/s42255-020-0191-z
24. Samuels Y, Wang Z, Bardelli A, *et al*. High frequency of mutations of the PIK3CA gene in human cancers. *Science.* 2004;304(5670):554.
doi: 10.1126/science.1096502
25. Jia J, Zhang W, Wang B, Trinko R, Jiang J. The *Drosophila* Ste20 family kinase dMST functions as a tumor suppressor by restricting cell proliferation and promoting apoptosis. *Genes Dev.* 2003;17(20):2514-2519.
doi: 10.1101/gad.1134003
26. Wu S, Huang J, Dong J, Pan D. Hippo encodes a Ste-20 family protein kinase that restricts cell proliferation and promotes apoptosis in conjunction with Salvador and warts. *Cell.* 2003;114(4):445-456.
doi: 10.1016/s0092-8674(03)00549-x
27. Zhou B, Lin W, Long Y, *et al*. Notch signaling pathway: Architecture, disease, and therapeutics. *Signal Transduct Target Ther.* 2022;7(1):95.
doi: 10.1038/s41392-022-00934-y
28. Spana EP, Kopczynski C, Goodman CS, *et al*. Asymmetric localization of numb autonomously determines sibling neuron identity in the *Drosophila* CNS. *Development.* 1995;121(11):3489-3494.
doi: 10.1242/dev.121.11.3489
29. Porter PL, Malone KE, Heagerty PJ, *et al*. Expression of cell-cycle regulators p27Kip1 and cyclin E, alone and in combination, correlate with survival in young breast cancer patients. *Nat Med.* 1997;3(2):222-225.
doi: 10.1038/nm0297-222
30. Malumbres M, Barbacid M. To cycle or not to cycle: A critical decision in cancer. *Nat Rev Cancer*. 2001;1(3):222-231.
doi: 10.1038/35106065
31. Bowman SK, Neumuller RA, Novatchkova M, *et al*. The *Drosophila* NuMA Homolog Mud regulates spindle orientation in asymmetric cell division. *Dev Cell.* 2006;10(6):731-742.
doi: 10.1016/j.devcel.2006.05.005
32. Izumi, Y, Ohta N, Hisata K, Raabe T, Matsuzaki F. *Drosophila* Pins-binding protein Mud regulates spindle-polarity coupling and centrosome organization. *Nat Cell Biol.* 2006;8(6):586-593.
doi: 10.1038/ncb1409
33. Lee CY, Andersen RO, Cabernard C, *et al*. *Drosophila* aurora-A kinase inhibits neuroblast self-renewal by regulating aPKC/Numb cortical polarity and spindle orientation. *Genes Dev.* 2006;20(24):3464-3474.
doi: 10.1101/gad.1489406
34. Siller KH, Cabernard C, Doe CQ. The NuMA-related Mud protein binds Pins and regulates spindle orientation in *Drosophila* neuroblasts. *Nat Cell Biol.* 2006;8(6):594-600.
doi: 10.1038/ncb1412
35. Wang H, Somers GW, Bashirullah A, *et al*. Aurora-A acts as a tumor suppressor and regulates self-renewal of *Drosophila* neuroblasts. *Genes Dev.* 2006;20(24):3453-3463.
doi: 10.1101/gad.1487506
36. Wang H, Ouyang Y, Somers WG, *et al*. Polo inhibits progenitor self-renewal and regulates Numb asymmetry by phosphorylating Pon. *Nature.* 2007;449(7158):96-100.
doi: 10.1038/nature06056
37. Cabernard C, Doe CQ. Apical/basal spindle orientation is required for neuroblast homeostasis and neuronal differentiation in *Drosophila*. *Dev Cell.* 2009;17(1):134-141.
doi: 10.1016/j.devcel.2009.06.009
38. Gomez-Lopez S, Lerner RG, Petritsch C. Asymmetric cell division of stem and progenitor cells during homeostasis and cancer. *Cell Mol Life Sci.* 2014;71(4):575-597.
doi: 10.1007/s00018-013-1386-1
39. Hartenstein V, Campos-Ortega JA. Early neurogenesis in wild-type *Drosophila* melanogaster. *Wilehm Roux Arch Dev Biol.* 1984;193(5):308-325.
doi: 10.1007/BF00848159
40. Thiery JP, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. *Cell.* 2009;139(5):871-890.
doi: 10.1016/j.cell.2009.11.007
41. Martin AC, Kaschube M, Wieschaus EF. Pulsed contractions of an actin-myosin network drive apical constriction. *Nature.* 2009;457(7228):495-499.
doi: 10.1038/nature07522
42. Sidor C, Roper K. Squeezing out in a "tug of war": The role of myosin in neural stem cell delamination. *J Cell Biol.* 2017;216(5):1215-1218.
doi: 10.1083/jcb.201702116
43. Simoes S, Oh Y, Wang MFZ, Fernandez-Gonzalez R, Tepass U. Myosin II promotes the anisotropic loss of the apical domain during *Drosophila* neuroblast ingression. *J Cell Biol.* 2017;216(5):1387-1404.
doi: 10.1083/jcb.201608038
44. Wang F, Dumstrei K, Haag T, Hartenstein V. The role of

DE-cadherin during cellularization, germ layer formation and early neurogenesis in the *Drosophila* embryo. *Dev Biol.* 2004;270(2): 350-363.
doi: 10.1016/j.ydbio.2004.03.002

45. Hartenstein V, Younossi-Hartenstein A, Lekven A. Delamination and division in the *Drosophila* neurectoderm: Spatiotemporal pattern, cytoskeletal dynamics, and common control by neurogenic and segment polarity genes. *Dev Biol.* 1994;165(2):480-499.
doi: 10.1006/dbio.1994.1269
46. Arefin B, Parvin F, Bahrampour S, Stadler CB, Thor S. *Drosophila* neuroblast selection is gated by notch, snail, SoxB, and EMT gene interplay. *Cell Rep.* 2019;29(11):3636-3651.e3.
doi: 10.1016/j.celrep.2019.11.038
47. Sasaki N, Sasamura T, Ishikawa HO, *et al*. Polarized exocytosis and transcytosis of Notch during its apical localization in *Drosophila* epithelial cells. *Genes Cells.* 2007;12(1):89-103.
doi: 10.1111/j.1365-2443.2007.01037.x
48. Hatakeyama J, Wakamatsu Y, Nagafuchi A, *et al*. Cadherin-based adhesions in the apical endfoot are required for active Notch signaling to control neurogenesis in vertebrates. *Development.* 2014;141(8):1671-1682.
doi: 10.1242/dev.102988
49. Loh CY, Chai JY, Tang TF, *et al*. The E-Cadherin and N-Cadherin Switch in epithelial-to-mesenchymal transition: Signaling, therapeutic implications, and challenges. *Cells.* 2019;8(10):1118.
doi: 10.3390/cells8101118
50. Huang Z, Zhang Z, Zhou C, Liu L, Huang C. Epithelial-mesenchymal transition: The history, regulatory mechanism, and cancer therapeutic opportunities. *MedComm (2020)*. 2022;3(2):e144.
doi: 10.1002/mco2.144
51. Cai Y, Chia W, Yang X. A family of snail-related zinc finger proteins regulates two distinct and parallel mechanisms that mediate *Drosophila* neuroblast asymmetric divisions. *EMBO J.* 2001;20(7):1704-1714.
doi: 10.1093/emboj/20.7.1704
52. Frixen UH, Behrens J, Sachs M, *et al*. E-cadherin-mediated cell-cell adhesion prevents invasiveness of human carcinoma cells. *J Cell Biol.* 1991;113(1):173-185.
doi: 10.1083/jcb.113.1.173
53. Vleminckx K, Vakaet L Jr., Mareel M, Fiers W, Van Roy F. Genetic manipulation of E-cadherin expression by epithelial tumor cells reveals an invasion suppressor role. *Cell.* 1991;66(1):107-119.
doi: 10.1016/0092-8674(91)90143-m
54. Rosso M, Majem B, Devis L, *et al*. E-cadherin: A determinant molecule associated with ovarian cancer progression, dissemination and aggressiveness. *PLoS One.* 2017;12(9):e0184439.
doi: 10.1371/journal.pone.0184439
55. Lewis-Tuffin LJ, Rodriguez F, Giannini C, *et al*. Misregulated E-cadherin expression associated with an aggressive brain tumor phenotype. *PLoS One.* 2010;5(10):e13665.
doi: 10.1371/journal.pone.0013665
56. Tanaka H, Kono E, Tran CP, *et al*. Monoclonal antibody targeting of N-cadherin inhibits prostate cancer growth, metastasis and castration resistance. *Nat Med.* 2010;16(12):1414-1420.
doi: 10.1038/nm.2236
57. Putzke AP, Ventura AP, Bailey AM, *et al*. Metastatic progression of prostate cancer and e-cadherin regulation by zeb1 and SRC family kinases. *Am J Pathol.* 2011;179(1):400-410.
doi: 10.1016/j.ajpath.2011.03.028
58. Noseda M, McLean G, Niessen K, *et al*. Notch activation results in phenotypic and functional changes consistent with endothelial-to-mesenchymal transformation. *Circ Res.* 2004;94(7):910-917.
doi: 10.1161/01.RES.0000124300.76171.C9
59. Timmerman LA, Grego-Bessa J, Raya A, *et al*. Notch promotes epithelial-mesenchymal transition during cardiac development and oncogenic transformation. *Genes Dev.* 2004;18(1):99-115.
doi: 10.1101/gad.276304
60. Zavadil J, Cermak L, Soto-Nieves N, *et al*. Integration of TGF-beta/Smad and Jagged1/Notch signalling in epithelial-to-mesenchymal transition. *EMBO J.* 2004;23(5):1155-1165.
doi: 10.1038/sj.emboj.7600069
61. Sahlgren C, Gustafsson MV, Jin S, Poellinger L, Lendahl U. Notch signaling mediates hypoxia-induced tumor cell migration and invasion. *Proc Natl Acad Sci U S A.* 2008;105(17): 6392-6397.
doi: 10.1073/pnas.0802047105
62. Meisel CT, Porcheri C, Mitsiadis TA. Cancer stem cells, quo Vadis? The notch signaling pathway in tumor initiation and progression. *Cells.* 2020;9(8):1879.
doi: 10.3390/cells9081879
63. Moore G, Annett S, McClements L, Robson T. Top notch targeting strategies in cancer: A detailed overview of recent insights and current perspectives. *Cells.* 2020;9(6):1503.
doi: 10.3390/cells9061503
64. Akil A, Gutierrez-Garcia AK, Guenter R, Rose JB, Beck AW, Chen H, Ren B. Notch signaling in vascular endothelial cells, angiogenesis, and tumor progression: An update and prospective. *Front Cell Dev Biol.* 2021;9:642352.
doi: 10.3389/fcell.2021.642352
65. Edwards A, Brennan K. Notch signalling in breast development and cancer. *Front Cell Dev Biol.* 2021;9:692173.
doi: 10.3389/fcell.2021.692173
66. Misiorek JO, Przybyszewska-Podstawka A, Kalafut J, *et al*. Context matters: NOTCH signatures and pathway in cancer progression and metastasis. *Cells.* 2021;10(1):94.
doi: 10.3390/cells10010094
67. Tsao CM, Yan MD, Shih YL, *et al*. SOX1 functions as a tumor suppressor by antagonizing the WNT/beta-catenin signaling pathway in hepatocellular carcinoma. *Hepatology.* 2012;56(6):2277-2287.
doi: 10.1002/hep.25933
68. Lin YW, Tsao CM, Yu PN, Shih YL, Lin CH, Yan MD. SOX1 suppresses cell growth and invasion in cervical cancer. *Gynecol Oncol.* 2013;131(1):174-181.
doi: 10.1016/j.ygyno.2013.07.111
69. Lei XX, Liu Y, Wang JX, *et al*. SOX1 promotes differentiation

of nasopharyngeal carcinoma cells by activating retinoid metabolic pathway. *Cell Death Dis.* 2020;11(5):331. doi: 10.1038/s41419-020-2513-1
70. Wang D, Xiong F, Wu G, *et al*. MiR-155-5p suppresses SOX1 to promote proliferation of cholangiocarcinoma via RAF/MEK/ERK pathway. *Cancer Cell Int.* 2021;21(1):656. doi: 10.1186/s12935-021-02374-0
71. Garcia I, Aldaregia J, Marjanovic Vicentic J, *et al*. Oncogenic activity of SOX1 in glioblastoma. *Sci Rep.* 2017;7:46575. doi: 10.1038/srep46575
72. Bass AJ, Watanabe H, Mermel CH, *et al*. SOX2 is an amplified lineage-survival oncogene in lung and esophageal squamous cell carcinomas. *Nat Genet.* 2009;41(11):1238-1242. doi: 10.1038/ng.465
73. Cano A, Perez-Moreno MA, Rodrigo I, *et al*. The transcription factor snail controls epithelial-mesenchymal transitions by repressing E-cadherin expression. *Nat Cell Biol.* 2000;2(2):76-83. doi: 10.1038/35000025
74. Mezencev R, Matyunina LV, Jabbari N, *et al*. Snail-induced epithelial-to-mesenchymal transition of MCF-7 breast cancer cells: Systems analysis of molecular changes and their effect on radiation and drug sensitivity. *BMC Cancer.* 2016;16:236. doi: 10.1186/s12885-016-2274-5
75. Wang H, Wang Z, Li Y, *et al*. Silencing snail reverses epithelial-mesenchymal transition and increases radiosensitivity in hypopharyngeal carcinoma. *Onco Targets Ther.* 2020;13:497-511. doi: 10.2147/ott.s237410
76. Yastrebova MA, Khamidullina AI, Tatarskiy VV, Scherbakov AM. Snail-family proteins: Role in carcinogenesis and prospects for antitumor therapy. *Acta Naturae.* 2021;13(1):76-90. doi: 10.32607/actanaturae.11062
77. Swaminathan V, Mythreye K, O'Brien ET, Berchuck A, Blobe GC, Superfine R. Mechanical stiffness grades metastatic potential in patient tumor cells and in cancer cell lines. *Cancer Res.* 2011;71(15):5075-5080. doi: 10.1158/0008-5472.CAN-11-0247
78. Yuan X, Sipe CW, Suzawa M, Bland ML, Siegrist SE. Dilp-2-mediated PI3-kinase activation coordinates reactivation of quiescent neuroblasts with growth of their glial stem cell niche. *PLoS Biol.* 2020;18(5):e3000721. doi: 10.1371/journal.pbio.3000721
79. Sood C, Justis VT, Doyle SE, Siegrist SE. Notch signaling regulates neural stem cell quiescence entry and exit in *Drosophila*. *Development.* 2022;149(4):dev200275. doi: 10.1242/dev.200275
80. Ding R, Weynans K, Bossing T, Barros CS, Berger C. The Hippo signalling pathway maintains quiescence in *Drosophila* neural stem cells. *Nat Commun.* 2016;7:10510. doi: 10.1038/ncomms10510
81. Dong J, Feldmann G, Huang J, *et al*. Elucidation of a universal size-control mechanism in *Drosophila* and mammals. *Cell.* 2007;130(6):1120-1133. doi: 10.1016/j.cell.2007.07.019
82. Oh H, Irvine KD. *In vivo* regulation of Yorkie phosphorylation and localization. *Development.* 2008;135(6):1081-1088. doi: 10.1242/dev.015255
83. Nishioka K, Rice JC, Sarma K, *et al*. PR-Set7 is a nucleosome-specific methyltransferase that modifies lysine 20 of histone H4 and is associated with silent chromatin. *Mol Cell.* 2002;9(6):1201-1213. doi: 10.1016/s1097-2765(02)00548-8
84. Sakaguchi A, Steward R. Aberrant monomethylation of histone H4 lysine 20 activates the DNA damage checkpoint in *Drosophila* melanogaster. *J Cell Biol.* 2007;176(2):155-162. doi: 10.1083/jcb.200607178
85. Huang J, Gujar MR, Deng Q, *et al*. Histone lysine methyltransferase Pr-set7/SETD8 promotes neural stem cell reactivation. *EMBO Rep.* 2021;22(4):e50994. doi: 10.15252/embr.202050994
86. Santamaria D, Barrière C, Cerqueira A, *et al*. Cdk1 is sufficient to drive the mammalian cell cycle. *Nature.* 2007;448(7155):811-815. doi: 10.1038/nature06046
87. Benchabane H, Xin N, Tian A, *et al*. Jerky/Earthbound facilitates cell-specific Wnt/Wingless signalling by modulating beta-catenin-TCF activity. *EMBO J.* 2011;30(8):1444-1458. doi: 10.1038/emboj.2011.67
88. Ding WY, Huang J, Wang H. Waking up quiescent neural stem cells: Molecular mechanisms and implications in neurodevelopmental disorders. *PLoS Genet.* 2020;16(4):e1008653. doi: 10.1371/journal.pgen.1008653
89. Stemke-Hale K, Gonzalez-Angulo AM, Lluch A, *et al*. An integrative genomic and proteomic analysis of PIK3CA, PTEN, and AKT mutations in breast cancer. *Cancer Res.* 2008;68(15):6084-6091. doi: 10.1158/0008-5472.CAN-07-6854
90. Zhang J, Roberts TM, Shivdasani RA. Targeting PI3K signaling as a therapeutic approach for colorectal cancer. *Gastroenterology.* 2011;141(1):50-61. doi: 10.1053/j.gastro.2011.05.010
91. Cancer Genome Atlas Research N. Comprehensive genomic characterization of squamous cell lung cancers. *Nature.* 2012;489(7417):519-525. doi: 10.1038/nature11404
92. Lui VW, Hedberg ML, Li H, *et al*. Frequent mutation of the PI3K pathway in head and neck cancer defines predictive biomarkers. *Cancer Discov.* 2013;3(7):761-769. doi: 10.1158/2159-8290.CD-13-0103
93. Feng X, Zhang M, Wang B, *et al*. CRABP2 regulates invasion and metastasis of breast cancer through hippo pathway dependent on ER status. *J Exp Clin Cancer Res.* 2019;38(1):361. doi: 10.1186/s13046-019-1345-2
94. Gobbi G, Donati B, Do Valle IF, *et al*. The Hippo pathway modulates resistance to BET proteins inhibitors in lung cancer cells. *Oncogene.* 2019;38(42):6801-6817. doi: 10.1038/s41388-019-0924-1
95. Feng X, Lu T, Li J, *et al*. The tumor suppressor interferon regulatory factor 2 Binding protein 2 regulates hippo pathway in liver cancer by a feedback loop in mice. *Hepatology.* 2020;71(6):1988-2004. doi: 10.1002/hep.30961

96. Wang X, Sun D, Tai J, Chen S, Hong S, Wang L. ZNF280A promotes proliferation and tumorigenicity via inactivating the hippo-signaling pathway in colorectal cancer. *Mol Ther Oncolytics.* 2019;12:204-213. doi: 10.1016/j.omto.2019.01.002
97. Overholtzer M, Zhang J, Smolen GA, *et al*. Transforming properties of YAP, a candidate oncogene on the chromosome 11q22 amplicon. *Proc Natl Acad Sci U S A.* 2006;103(33):12405-12410. doi: 10.1073/pnas.0605579103
98. Zender L, Spector MS, Xue W, *et al*. Identification and validation of oncogenes in liver cancer using an integrative oncogenomic approach. *Cell.* 2006;125(7):1253-1267. doi: 10.1016/j.cell.2006.05.030
99. Jiao S, Guan J, Chen M, *et al*. Targeting IRF3 as a YAP agonist therapy against gastric cancer. *J Exp Med.* 2018;215(2): 699-718. doi: 10.1084/jem.20171116
100. Shen J, Cao B, Wang Y, *et al*. Hippo component YAP promotes focal adhesion and tumour aggressiveness via transcriptionally activating THBS1/FAK signalling in breast cancer. *J Exp Clin Cancer Res.* 2018;37(1):175. doi: 10.1186/s13046-018-0850-z
101. Jin D, Guo J, Wu Y, *et al*. m^{6}A demethylase ALKBH5 inhibits tumor growth and metastasis by reducing YTHDFs-mediated YAP expression and inhibiting miR-107/LATS2-mediated YAP activity in NSCLC. *Mol Cancer.* 2020;19(1):40. doi: 10.1186/s12943-020-01161-1
102. Levy D, Adamovich Y, Reuven N, Shaul Y. The Yes-associated protein 1 stabilizes p73 by preventing Itch-mediated ubiquitination of p73. *Cell Death Differ.* 2007;14(4):743-751. doi: 10.1038/sj.cdd.4402063
103. Yuan M, Tomlinson V, Lara R, *et al*. Yes-associated protein (YAP) functions as a tumor suppressor in breast. *Cell Death Differ.* 2008;15(11):1752-1759. doi: 10.1038/cdd.2008.108
104. Ehsanian R, Brown M, Lu H, *et al*. YAP dysregulation by phosphorylation or DeltaNp63-mediated gene repression promotes proliferation, survival and migration in head and neck cancer subsets. *Oncogene.* 2010;29(46):6160-6171. doi: 10.1038/onc.2010.339
105. Cottini F, Hideshima T, Xu C, *et al*. Rescue of Hippo coactivator YAP1 triggers DNA damage-induced apoptosis in hematological cancers. *Nat Med.* 2014;20(6):599-606. doi: 10.1038/nm.3562
106. Ravindran Menon D, Luo Y, Arcaroli JJ, *et al*. CDK1 interacts with Sox2 and promotes tumor initiation in human melanoma. *Cancer Res.* 2018;78(23):6561-6574. doi: 10.1158/0008-5472.CAN-18-0330
107. Wu CX, Wang XQ, Chok SH, *et al*. Blocking CDK1/PDK1/beta-Catenin signaling by CDK1 inhibitor RO3306 increased the efficacy of sorafenib treatment by targeting cancer stem cells in a preclinical model of hepatocellular carcinoma. *Theranostics.* 2018;8(14):3737-3750. doi: 10.7150/thno.25487
108. Zhang P, Kawakami H, Liu W, *et al*. Targeting CDK1 and MEK/ERK overcomes apoptotic resistance in BRAF-mutant human colorectal cancer. *Mol Cancer Res.* 2018;16(3):378-389. doi: 10.1158/1541-7786.mcr-17-0404
109. Qian JY, Gao J, Sun X, *et al*. KIAA1429 acts as an oncogenic factor in breast cancer by regulating CDK1 in an N6-methyladenosine-independent manner. *Oncogene.* 2019;38(33):6123-6141. doi: 10.1038/s41388-019-0861-z
110. Tian Z, Cao S, Li C, *et al*. LncRNA PVT1 regulates growth, migration, and invasion of bladder cancer by miR-31/CDK1. *J Cell Physiol.* 2019;234(4):4799-4811. doi: 10.1002/jcp.27279
111. Li M, He F, Zhang Z, *et al*. CDK1 serves as a potential prognostic biomarker and target for lung cancer. *J Int Med Res.* 2020;48(2):300060519897508. doi: 10.1177/0300060519897508
112. Chen H, Hu K, Xie Y, *et al*. CDK1 promotes epithelial-mesenchymal transition and migration of head and neck squamous carcinoma cells by repressing Δnp63alpha-mediated transcriptional regulation. *Int J Mol Sci.* 2022;23(13):7385. doi: 10.3390/ijms23137385
113. Ohba S, Tang Y, Johannessen TA, Mukherjee J. PKM2 interacts with the Cdk1-CyclinB complex to facilitate cell cycle progression in Gliomas. *Front Oncol.* 2022;12:844861. doi: 10.3389/fonc.2022.844861
114. Li Y, Sun L, Zhang Y, *et al*. The histone modifications governing TFF1 transcription mediated by estrogen receptor. *J Biol Chem*. 2011;286(16):13925-13936. doi: 10.1074/jbc.M111.223198
115. Li Z, Nie F, Wang S, Li L. Histone H4 Lys 20 monomethylation by histone methylase SET8 mediates Wnt target gene activation. *Proc Natl Acad Sci U S A.* 2011;108(8):3116-3123. doi: 10.1073/pnas.1009353108
116. Pascual J, Turner NC. Targeting the PI3-kinase pathway in triple-negative breast cancer. *Ann Oncol.* 2019;30(7): 1051-1060. doi: 10.1093/annonc/mdz133
117. Calvet L, Dos-Santos O, Spanakis E, *et al*. YAP1 is essential for malignant mesothelioma tumor maintenance. *BMC Cancer.* 2022;22(1):639. doi: 10.1186/s12885-022-09686-y
118. Qadir J, Li F, Yang BB. Circular RNAs modulate Hippo-YAP signaling: Functional mechanisms in cancer. *Theranostics.* 2022;12(9):4269-4287. doi: 10.7150/thno.71708
119. Otsuki L, Brand AH. Cell cycle heterogeneity directs the timing of neural stem cell activation from quiescence. *Science.* 2018;360(6384):99-102. doi: 10.1126/science.aan8795
120. Knoblich JA. Mechanisms of asymmetric stem cell division. *Cell.* 2008;132(4):583-597. doi: 10.1016/j.cell.2008.02.007
121. De Torres-Jurado A, Manzanero-Ortiz S, Carmena A. Glial-secreted Netrins regulate Robo1/Rac1-Cdc42 signaling threshold levels during *Drosophila* asymmetric neural stem/progenitor cell division. *Curr Biol*. 2022;32(10):2174-2188.e3. doi: 10.1016/j.cub.2022.04.001
122. Kraut R, Campos-Ortega JA. Inscuteable, a neural precursor

gene of *Drosophila*, encodes a candidate for a Cytoskeleton adaptor protein. *Dev Biol.* 1996;174(1):65-81.
doi: 10.1006/dbio.1996.0052

123. Hirata J, Nakagoshi H, Nabeshima Y, *et al*. Asymmetric segregation of the homeodomain protein Prospero during *Drosophila* development. *Nature.* 1995;377(6550):627-630.
doi: 10.1038/377627a0

124. Knoblich JA, Jan LY, Jan YN. Asymmetric segregation of numb and Prospero during cell division. *Nature.* 1995;377(6550):624-627.
doi: 10.1038/377624a0

125. Spana EP, Doe CQ. The prospero transcription factor is asymmetrically localized to the cell cortex during neuroblast mitosis in *Drosophila*. *Development.* 1995;121(10):3187-3195.
doi: 10.1242/dev.121.10.3187

126. Broadus J, Fuerstenberg S, Doe CQ. Staufen-dependent localization of prospero mRNA contributes to neuroblast daughter-cell fate. *Nature.* 1998;391(6669):792-795.
doi: 10.1038/35861

127. Betschinger J, Mechtler K, Knoblich JA. Asymmetric segregation of the tumor suppressor brat regulates self-renewal in *Drosophila* neural stem cells. *Cell.* 2006;124(6):1241-1253.
doi: 10.1016/j.cell.2006.01.038

128. Arama E, Dickman D, Kimchie Z, Shearn A, Lev Z. Mutations in the beta-propeller domain of the *Drosophila* brain tumor (brat) protein induce neoplasm in the larval brain. *Oncogene.* 2000;19(33):3706-3716.
doi: 10.1038/sj.onc.1203706

129. Bello B, Reichert H, Hirth F. The brain tumor gene negatively regulates neural progenitor cell proliferation in the larval central brain of *Drosophila*. *Development.* 2006;133(14): 2639-2648.
doi: 10.1242/dev.02429

130. Lee CY, Wilkinson BD, Siegrist SE, Wharton RP, Doe CQ. Brat is a Miranda cargo protein that promotes neuronal differentiation and inhibits neuroblast self-renewal. *Dev Cell.* 2006;10(4):441-449.
doi: 10.1016/j.devcel.2006.01.017

131. Carmena A. Compromising asymmetric stem cell division in *Drosophila* central brain: Revisiting the connections with tumorigenesis. *Fly (Austin)*. 2018;12(1):71-80.
doi: 10.1080/19336934.2017.1416277

132. Chen G, Kong J, Tucker-Burden C, *et al*. Human Brat ortholog TRIM3 is a tumor suppressor that regulates asymmetric cell division in glioblastoma. *Cancer Res.* 2014;74(16):4536-4548.
doi: 10.1158/0008-5472.can-13-3703

133. Mukherjee S, Tucker-Burden C, Zhang C, *et al*. *Drosophila* brat and human ortholog TRIM3 maintain stem cell equilibrium and suppress brain tumorigenesis by attenuating notch nuclear transport. *Cancer Res.* 2016;76(8):2443-2452.
doi: 10.1158/0008-5472.CAN-15-2299

134. Guo M, Jan LY, Jan YN. Control of daughter cell fates during asymmetric division: Interaction of Numb and Notch. *Neuron.* 1996;17(1):27-41.
doi: 10.1016/s0896-6273(00)80278-0

135. Bhat KM. Notch signaling acts before cell division to promote asymmetric cleavage and cell fate of neural precursor cells. *Sci Signal.* 2014;7(348):ra101.
doi: 10.1126/scisignal.2005317

136. Choi HY, Seok J, Kang GH, Lim KM, Cho SG. The role of NUMB/NUMB isoforms in cancer stem cells. *BMB Rep.* 2021;54(7):335-343.
doi: 10.5483/BMBRep.2021.54.7.048

137. Ke S, Lu S, Wang C, *et al*. Comprehensive analysis of the prognostic value and functions of prefoldins in hepatocellular carcinoma. *Front Mol Biosci.* 2022;9:957001.
doi: 10.3389/fmolb.2022.957001

138. Woods DF, Bryant PJ. The discs-large tumor suppressor gene of *Drosophila* encodes a guanylate kinase homolog localized at septate junctions. *Cell.* 1991;66(3):451-464.
doi: 10.1016/0092-8674(81)90009-x

139. Kraut R, Chia W, Jan LY, Jan YN, Knoblich JA. Role of inscuteable in orienting asymmetric cell divisions in *Drosophila*. *Nature.* 1996;383(6595):50-55.
doi: 10.1038/383050a0

140. Kuchinke U, Grawe F, Knust E. Control of spindle orientation in *Drosophila* by the Par-3-related PDZ-domain protein Bazooka. *Curr Biol.* 1998;8(25):1357-1365.
doi: 10.1016/s0960-9822(98)00016-5

141. Wodarz A, Ramrath A, Kuchinke U, Knust E. Bazooka provides an apical cue for Inscuteable localization in *Drosophila* neuroblasts. *Nature.* 1999;402(6761):544-547.
doi: 10.1038/990128

142. Ohshiro T,Yagami T, Zhang C, Matsuzaki F. Role of cortical tumour-suppressor proteins in asymmetric division of *Drosophila* neuroblast. *Nature.* 2000;408(6812):593-596.
doi: 10.1038/35046087

143. Petronczki M, Knoblich JA. DmPAR-6 directs epithelial polarity and asymmetric cell division of neuroblasts in *Drosophila*. *Nat Cell Biol.* 2001;3(1):43-49.
doi: 10.1038/35050550

144. Albertson R, Doe CQ. Dlg, Scrib and Lgl regulate neuroblast cell size and mitotic spindle asymmetry. *Nat Cell Biol.* 2003;5(2):166-170.
doi: 10.1038/ncb922

145. Wang H, Cai Y, Chia W, Yang X. *Drosophila* homologs of mammalian TNF/TNFR-related molecules regulate segregation of Miranda/Prospero in neuroblasts. *EMBO J.* 2006;25(24):5783-5793.
doi: 10.1038/sj.emboj.7601461

146. Wang L, Zhang H, Hasim A, *et al*. Partition-defective 3 (PARD3) regulates proliferation, apoptosis, migration, and invasion in esophageal squamous cell carcinoma cells. *Med Sci Monit.* 2017;23:2382-2390.
doi: 10.12659/msm.903380

147. Marques E, Englund JI, Tervonen TA, *et al*. Par6G suppresses cell proliferation and is targeted by loss-of-function mutations in multiple cancers. *Oncogene.* 2016;35(11):1386-1398.
doi: 10.1038/onc.2015.196

148. Sarkar S, Bristow CA, Dey P, *et al*. PRKCI promotes immune suppression in ovarian cancer. *Genes Dev.* 2017;31(11): 1109-1121.
doi: 10.1101/gad.296640.117

149. Wu Z, Huang C, Li R, Li H, Lu H, Lin Z. PRKCI mediates radiosensitivity via the hedgehog/gli1 pathway in cervical *Cancer*. Front Oncol. 2022;12:887139. doi: 10.3389/fonc.2022.887139
150. Liu Y, Yin N, Wang X, *et al*. Chromosome 3q26 gain is an early event driving coordinated overexpression of the PRKCI, SOX2, and ECT2 Oncogenes in lung squamous cell carcinoma. *Cell Rep.* 2020;30(3):771-782.e6. doi: 10.1016/j.celrep.2019.12.071
151. Zhaoran S, Weidong J. INSC is a prognosis-associated biomarker involved in tumor immune infiltration in colon adenocarcinoma. *Biomed Res Int.* 2022;2022:5794150. doi: 10.1155/2022/5794150
152. Culurgioni S, Mari S, Bonetti P, *et al*. Insc: LGN tetramers promote asymmetric divisions of mammary stem cells. *Nat Commun.* 2018;9(1):1025. doi: 10.1038/s41467-018-03343-4
153. Sun J, Huang J, Lan J, *et al*. Overexpression of CENPF correlates with poor prognosis and tumor bone metastasis in breast cancer. *Cancer Cell Int.* 2019;19:264. doi: 10.1186/s12935-019-0986-8
154. Yu B, Chen L, Zhang W, *et al.* TOP2A and CENPF are synergistic master regulators activated in cervical cancer. *BMC Med Genomics.* 2020;13(1):145. doi: 10.1186/s12920-020-00800-2
155. Huang Y, Chen X, Wang L, Wang T, Tang X, Su X. Centromere protein F (CENPF) serves as a potential prognostic biomarker and target for human hepatocellular carcinoma. *J Cancer.* 2021;12(10):2933-2951. doi: 10.7150/jca.52187
156. Li MX, Zhang MY, Dong HH, *et al*. Overexpression of CENPF is associated with progression and poor prognosis of lung adenocarcinoma. *Int J Med Sci.* 2021;18(2):494-504. doi: 10.7150/ijms.49041
157. Huang YG, Li D, Wang L, Su XM, Tang XB. CENPF/CDK1 signaling pathway enhances the progression of adrenocortical carcinoma by regulating the G2/M-phase cell cycle. *J Transl Med.* 2022;20(1):78. doi: 10.1186/s12967-022-03277-y
158. Deng M, Liu B, Zhang Z, *et al*. Knockdown of G-protein-signaling modulator 2 promotes metastasis of non-small-cell lung cancer by inducing the expression of Snail. *Cancer Sci.* 2020;111(9):3210-3221. doi: 10.1111/cas.14519
159. Yang D, Ji F, Li Y, *et al*. GPSM2 serves as an independent prognostic biomarker for liver cancer survival. *Technol Cancer Res Treat.* 2020;19:1533033820945817. doi: 10.1177/1533033820945817
160. Zhou X, Dang S, Jiang H, *et al*. Identification of G-protein signaling modulator 2 as a diagnostic and prognostic biomarker of pancreatic adenocarcinoma: An exploration of its regulatory mechanisms. *J Gastrointest Oncol.* 2021;12(3):1164-1179. doi: 10.21037/jgo-21-224
161. Stewart M, Murphy C, Fristrom JW. The recovery and preliminary characterization of X chromosome mutants affecting imaginal discs of *Drosophila* melanogaster. *Dev Biol.* 1972;27(1):71-83. doi: 10.1016/0012-1606(72)90113-3
162. Gateff E, Schneiderman HA. Developmental capacities of benign and malignant neoplasms of Drosophila. *Wilhelm Roux Arch Entwickl Mech Org.* 1974;176(1):23-65. doi: 10.1007/BF00577830
163. Gateff E. Malignant neoplasms of genetic origin in *Drosophila* melanogaster. *Science.* 1978;200(4349):1448-1459. doi: 10.1126/science.96525
164. Bilder D, Perrimon N. Localization of apical epithelial determinants by the basolateral PDZ protein Scribble. *Nature.* 2000;403(6770):676-680. doi: 10.1038/35001108
165. Pearson HB, Perez-Mancera PA, Dow LE, *et al*. SCRIB expression is deregulated in human prostate cancer, and its deficiency in mice promotes prostate neoplasia. *J Clin Invest*. 2011;121(11):4257-4267. doi: 10.1172/JCI58509
166. Anastas JN, Biechele TL, Robitaille M, *et al*. A protein complex of SCRIB, NOS1AP and VANGL1 regulates cell polarity and migration, and is associated with breast cancer progression. *Oncogene.* 2012;31(32):3696-3708. doi: 10.1038/onc.2011.528
167. Stephens R, Lim K, Portela M, Kvansakul M, Humbert PO, Richardson HE. The scribble cell polarity module in the regulation of cell signaling in tissue development and tumorigenesis. *J Mol Biol.* 2018;430(19):3585-3612. doi: 10.1016/j.jmb.2018.01.011
168. Carmena A. The case of the scribble polarity module in asymmetric neuroblast division in development and tumorigenesis. *Int J Mol Sci.* 2020;21(8):2865. doi: 10.3390/ijms21082865
169. Vainberg IE, Lewis SA, Rommelaere H, *et al*. Prefoldin, a chaperone that delivers unfolded proteins to cytosolic chaperonin. *Cell.* 1998;93(5):863-873. doi: 10.1016/s0092-8674(00)81446-4
170. Zhang Y, Rai M, Wang C, Gonzalez C, Wang H. Prefoldin and Pins synergistically regulate asymmetric division and suppress dedifferentiation. *Sci Rep.* 2016;6:23735. doi: 10.1038/srep23735
171. Herranz-Montoya I, Park S, Djouder N. A comprehensive analysis of prefoldins and their implication in cancer. *iScience.* 2021;24(11):103273. doi: 10.1016/j.isci.2021.103273
172. Wang P, Zhao J, Yang X, *et al*. PFDN1, an indicator for colorectal cancer prognosis, enhances tumor cell proliferation and motility through cytoskeletal reorganization. *Med Oncol.* 2015;32(12):264. doi: 10.1007/s12032-015-0710-z
173. Wang D, Shi W, Tang Y, *et al*. Prefoldin 1 promotes EMT and lung cancer progression by suppressing cyclin A expression. *Oncogene.* 2017;36(7):885-898. doi: 10.1038/onc.2016.257
174. Zhou C, Guo Z, Xu L, *et al*. PFND1 predicts poor prognosis of gastric cancer and promotes cell metastasis by activating the Wnt/beta-catenin pathway. *Onco Targets Ther.* 2020;13: 3177-3186 doi: 10.2147/ott.s236929

175. Riester M, Werner L, Bellmunt J, *et al*. Integrative analysis of 1q23.3 copy-number gain in metastatic urothelial carcinoma. *Clin Cancer Res.* 2014;20(7):1873-1883. doi: 10.1158/1078-0432.ccr-13-0759
176. Yesseyeva G, Aikemu B, Hong H, *et al*. Prefoldin subunits (PFDN1-6) serve as poor prognostic markers in gastric cancer. *Biosci Rep.* 2020;40(2):BSR20192712. doi: 10.1042/bsr20192712
177. Spana EP, Doe CQ. Numb antagonizes Notch signaling to specify sibling neuron cell fates. *Neuron.* 1996;17(1):21-26. doi: 10.1016/s0896-6273(00)80277-9
178. Buescher M, Yeo SL, Udolph G, *et al*. Binary sibling neuronal cell fate decisions in the *Drosophila* embryonic central nervous system are nonstochastic and require inscuteable-mediated asymmetry of ganglion mother cells. *Genes Dev.* 1998;12(12):1858-1870. doi: 10.1101/gad.12.12.1858
179. An H, Ge W, Xi Y, *et al*. Inscuteable maintains type I neuroblast lineage identity via Numb/Notch signaling in the *Drosophila* larval brain. *J Genet Genomics.* 2017;44(3):151-162. doi: 10.1016/j.jgg.2017.02.005
180. Wang NJ, Sanborn Z, Arnett KL, *et al*. Loss-of-function mutations in Notch receptors in cutaneous and lung squamous cell carcinoma. *Proc Natl Acad Sci U S A.* 2011;108(43):17761-17766. doi: 10.1073/pnas.1114669108
181. Gao YB, Chen ZL, Li JG, *et al*. Genetic landscape of esophageal squamous cell carcinoma. *Nat Genet.* 2014;46(10):1097-1102. doi: 10.1038/ng.3076
182. Rampias T, Vgenopoulou P, Avgeris M, *et al*. A new tumor suppressor role for the Notch pathway in bladder cancer. *Nat Med.* 2014;20(10):1199-1205. doi: 10.1038/nm.3678
183. Carmena A, Makarova A, Speicher S. The Rap1-Rgl-Ral signaling network regulates neuroblast cortical polarity and spindle orientation. *J Cell Biol.* 2011;195(4):553-562. doi: 10.1083/jcb.201108112
184. Li Q, Xu A, Chu Y, *et al*. Rap1A promotes esophageal squamous cell carcinoma metastasis through the AKT signaling pathway. *Oncol Rep.* 2019;42(5):1815-1824. doi: 10.3892/or.2019.7309
185. Keder A, Rives-Quinto N, Aerne BL, *et al*. The hippo pathway core cassette regulates asymmetric cell division. *Curr Biol.* 2015;25(21):2739-2750. doi: 10.1016/j.cub.2015.08.064
186. Justice RW, Zilian O, Woods DF, Noll M, Bryant PJ. The *Drosophila* tumor suppressor gene warts encodes a homolog of human myotonic dystrophy kinase and is required for the control of cell shape and proliferation. *Genes Dev.* 1995;9(5):534-546. doi: 10.1101/gad.9.5.534
187. Shen Z, Pan Y, Chen P, Jiang B, Fang X, Jiang Y. LATS1 exerts tumor suppressor functions via targeting Gli1 in colorectal cancer. *J Cancer.* 2021;12(24):7311-7319. doi: 10.7150/jca.62211
188. Marlow R, Strickland P, Lee JS, *et al*. SLITs suppress tumor growth *in vivo* by silencing Sdf1/Cxcr4 within breast epithelium. *Cancer Res.* 2008;68(19):7819-7827. doi: 10.1158/0008-5472.CAN-08-1357
189. Zhang C, Guo H, Li B, *et al*. Effects of Slit3 silencing on the invasive ability of lung carcinoma A549 cells. *Oncol Rep.* 2015;34(2):952-960. doi: 10.3892/or.2015.4031
190. Ng L, Chow AKM, Man JHW, *et al*. Suppression of Slit3 induces tumor proliferation and chemoresistance in hepatocellular carcinoma through activation of GSK3beta/beta-catenin pathway. *BMC Cancer.* 2018;18(1):621. doi: 10.1186/s12885-018-4326-5
191. Alebrahim D, Nayak M, Ward A, *et al*. Mapping semaphorins and netrins in the pathogenesis of human thoracic aortic aneurysms. *Int J Mol Sci.* 2019;20(9):2100. doi: 10.3390/ijms20092100
192. Jacob J, Maurange C, Gould AP. Temporal control of neuronal diversity: Common regulatory principles in insects and vertebrates? *Development*. 2008;135(21):3481-3489. doi: 10.1242/dev.016931
193. Brody T, Odenwald WF. Programmed transformations in neuroblast gene expression during *Drosophila* CNS lineage development. *Dev Biol.* 2000;226(1):34-44. doi: 10.1006/dbio.2000.9829
194. Isshiki T, Pearson B, Holbrook S, Doe CQ. *Drosophila* neuroblasts sequentially express transcription factors which specify the temporal identity of their neuronal progeny. *Cell.* 2001;106(4):511-521. doi: 10.1016/s0092-8674(01)00465-2
195. Baumgardt M, Karlsson D, Terriente J, Díaz-Benjumea FJ, Thor S. Neuronal subtype specification within a lineage by opposing temporal feed-forward loops. *Cell.* 2009;139(5):969-982. doi: 10.1016/j.cell.2009.10.032
196. Stanojevic D, Hoey T, Levine M. Sequence-specific DNA-binding activities of the gap proteins encoded by hunchback and Kruppel in *Drosophila*. *Nature.* 1989;341(6240):331-335. doi: 10.1038/341331a0
197. Mellerick DM, Kassis JA, Zhang SD, Zhang SD, Odenwald WF. Castor encodes a novel zinc finger protein required for the development of a subset of CNS neurons in *Drosophila*. *Neuron.* 1992;9(5):789-803. doi: 10.1016/0896-6273(92)90234-5
198. Yang X, Yeo S, Dick T, *et al*. The role of a *Drosophila* POU homeo domain gene in the specification of neural precursor cell identity in the developing embryonic central nervous system. *Genes Dev.* 1993;7(3):504-516. doi: 10.1101/gad.7.3.504
199. Cenci C, Gould AP. *Drosophila* Grainyhead specifies late programmes of neural proliferation by regulating the mitotic activity and Hox-dependent apoptosis of neuroblasts. *Development.* 2005;132(17):3835-3845. doi: 10.1242/dev.01932
200. Okano H, Temple S. Cell types to order: Temporal specification of CNS stem cells. *Curr Opin Neurobiol.* 2009;19(2):112-119. doi: 10.1016/j.conb.2009.04.003
201. Emery IF, Bedian V, Guild GM. Differential expression

of broad-complex transcription factors may forecast tissue-specific developmental fates during *Drosophila* metamorphosis. *Development.* 1994;120(11):3275-3287. doi: 10.1242/dev.120.11.3275

202. Zhu S, Lin S, Kao CF, Awasaki T, Chiang AS, Lee T. Gradients of the *Drosophila* Chinmo BTB-zinc finger protein govern neuronal temporal identity. *Cell.* 2006;127(2):409-422. doi: 10.1016/j.cell.2006.08.045
203. Dillon NR, Manning L, Hirono K, Doe CQ. Seven-up acts in neuroblasts to specify adult central complex neuron identity and initiate neuroblast decommissioning. *Development.* 2024;151(3):dev202504. doi: 10.1242/dev.202504
204. Bayraktar OA, Doe CQ. Combinatorial temporal patterning in progenitors expands neural diversity. *Nature.* 2013;498(7455):449-455. doi: 10.1038/nature12266
205. Ci W, Polo JM, Melnick A. B-cell lymphoma 6 and the molecular pathogenesis of diffuse large B-cell lymphoma. *Curr Opin Hematol.* 2008;15(4):381-390. doi: 10.1097/MOH.0b013e328302c7df
206. Ye BH, Lista F, Lo Coco F, *et al*. Alterations of a zinc finger-encoding gene, BCL-6, in diffuse large-cell lymphoma. *Science.* 1993;262(5134):747-750. doi: 10.1126/science.8235596
207. Alizadeh AA, Eisen MB, Davis RE, *et al*. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature*. 2000;403(6769):503-511. doi: 10.1038/35000501
208. Duan S, Cermak L, Pagan JK, *et al*. FBXO11 targets BCL6 for degradation and is inactivated in diffuse large B-cell lymphomas. *Nature.* 2012;481(7379):90-93. doi: 10.1038/nature10688
209. Bos R, Van Diest PJ, Van der Groep P, *et al*. Protein expression of B-cell lymphoma gene 6 (BCL-6) in invasive breast cancer is associated with cyclin D1 and hypoxia-inducible factor-1alpha (HIF-1alpha). *Oncogene.* 2003;22(55):8948-8951. doi: 10.1038/sj.onc.1206995
210. Logarajah S, Hunter P, Kraman M, *et al*. BCL-6 is expressed in breast cancer and prevents mammary epithelial differentiation. *Oncogene.* 2003;22(36):5572-5578. doi: 10.1038/sj.onc.1206689
211. Duy C, Hurtz C, Shojaee S, *et al*. BCL6 enables Ph+ acute lymphoblastic leukaemia cells to survive BCR-ABL1 kinase inhibition. *Nature.* 2011;473(7347):384-388. doi: 10.1038/nature09883
212. Hurtz C, Hatzi K, Cerchietti L, *et al*. BCL6-mediated repression of p53 is critical for leukemia stem cell survival in chronic myeloid leukemia. *J Exp Med.* 2011;208(11):2163-2174. doi: 10.1084/jem.20110304
213. Sato T, Tran TH, Peck AR, *et al*. Prolactin suppresses a progestin-induced CK5-positive cell population in luminal breast cancer through inhibition of progestin-driven BCL6 expression. *Oncogene.* 2014;33(17):2215-2224. doi: 10.1038/onc.2013.172
214. Kawabata KC, Zong H, Meydan C, *et al*. BCL6 maintains survival and self-renewal of primary human acute myeloid leukemia cells. *Blood.* 2021;137(6):812-825. doi: 10.1182/blood.2019001745
215. Li K, Liu Y, Ding Y, *et al*. BCL6 is regulated by the MAPK/ELK1 axis and promotes KRAS-driven lung cancer. *J Clin Invest.* 2022;132(22):e161308. doi: 10.1172/JCI161308
216. Walker SR Liu S, Xiang M, *et al*. The transcriptional modulator BCL6 as a molecular target for breast cancer therapy. *Oncogene.* 2015;34(9):1073-1082. doi: 10.1038/onc.2014.61
217. Cardenas MG, Oswald E, Yu W, Xue F, MacKerell AD Jr., Melnick AM. The expanding role of the BCL6 oncoprotein as a cancer therapeutic target. *Clin Cancer Res.* 2017;23(4):885-893. doi: 10.1158/1078-0432.CCR-16-2071
218. Hurtz C, Chan LN, Geng H, *et al*. Rationale for targeting BCL6 in MLL-rearranged acute lymphoblastic leukemia. *Genes Dev.* 2019;33(17-18):1265-1279. doi: 10.1101/gad.327593.119
219. Huang YH, Klingbeil O, He XY, *et al*. POU2F3 is a master regulator of a tuft cell-like variant of small cell lung cancer. *Genes Dev.* 2018;32(13-14):915-928. doi: 10.1101/gad.314815.118
220. Bintz J, Abuelafia AM, Gerbe F, *et al*. Expression of POU2F3 transcription factor control inflammation, immunological recruitment and metastasis of pancreatic cancer in mice. *Biology (Basel).* 2020;9(10):341. doi: 10.3390/biology9100341
221. Liu Z, Zhang X, Lei H, *et al*. CASZ1 induces skeletal muscle and rhabdomyosarcoma differentiation through a feed-forward loop with MYOD and MYOG. *Nat Commun.* 2020;11(1):911. doi: 10.1038/s41467-020-14684-4
222. Liu Z, Zhang X, Xu M, *et al*. Loss of CASZ1 tumor suppressor linked to oncogenic subversion of neuroblastoma core regulatory circuitry. *Cell Death Dis.* 2022;13(10):871. doi: 10.1038/s41419-022-05314-6
223. Wu YY, Chang CL, Chuang YJ, *et al*. CASZ1 is a novel promoter of metastasis in ovarian cancer. *Am J Cancer Res.* 2016;6(6):1253-1270.
224. Yuan M, Wang J, Fang F. Grainyhead-Like genes family may act as novel biomarkers in colon cancer. *Onco Targets Ther.* 2020;13:3237-3245. doi: 10.2147/OTT.S242763
225. He Y, Gan M, Wang Y, *et al*. EGFR-ERK induced activation of GRHL1 promotes cell cycle progression by upregulating cell cycle related genes in lung cancer. *Cell Death Dis.* 2021;12(5):430. doi: 10.1038/s41419-021-03721-9
226. Li M, Li Z, Guan X, *et al*. Suppressor gene GRHL1 is associated with prognosis in patients with oesophageal squamous cell carcinoma. *Oncol Lett.* 2019;17(5):4313-4320. doi: 10.3892/ol.2019.10072
227. Erdos E, Balint BL. NR2F2 orphan nuclear receptor is involved in estrogen receptor alpha-mediated transcriptional regulation in luminal a breast cancer cells. *Int J Mol Sci.* 2020;21(6):1910. doi: 10.3390/ijms21061910
228. Le Dily F, Metivier R, Gueguen MM, *et al*. COUP-TFI

modulates estrogen signaling and influences proliferation, survival and migration of breast cancer cells. *Breast Cancer Res Treat.* 2008;110(1):69-83.
doi: 10.1007/s10549-007-9693-6

229. Zhang C, Han Y, Huang H, *et al*. High NR2F2 transcript level is associated with increased survival and its expression inhibits TGF-beta-dependent epithelial-mesenchymal transition in breast cancer. *Breast Cancer Res Treat.* 2014;147(2):265-281. doi: 10.1007/s10549-014-3095-3
230. Xia B, Hou L, Kang H, *et al*. NR2F2 plays a major role in insulin-induced epithelial-mesenchymal transition in breast cancer cells. *BMC Cancer.* 2020;20(1):626. doi: 10.1186/s12885-020-07107-6
231. Lavallee VP, Gendron P, Lemieux S, *et al*. EVI1-rearranged acute myeloid leukemias are characterized by distinct molecular alterations. *Blood.* 2015;125(1):140-143. doi: 10.1182/blood-2014-07-591529
232. Hou A, Zhao L, Zhao F, *et al*. Expression of MECOM is associated with unfavorable prognosis in glioblastoma multiforme. *Onco Targets Ther.* 2016;9:315-320. doi: 10.2147/OTT.S95831
233. Bleu M, Mermet-Meillon F, Apfel V, *et al*. PAX8 and MECOM are interaction partners driving ovarian cancer. *Nat Commun.* 2021;12(1):2442. doi: 10.1038/s41467-021-22708-w
234. Elsherif M, Hammad M, Hafez H, *et al*. *MECOM* gene overexpression in pediatric patients with acute myeloid leukemia. *Acta Oncol.* 2022;61(4):516-522. doi: 10.1080/0284186X.2022.2025611
235. Li M, Ren H, Zhang Y, *et al*. MECOM/PRDM3 and PRDM16 Serve as prognostic-related biomarkers and are correlated with immune cell infiltration in lung adenocarcinoma. *Front Oncol.* 2022;12:772686. doi: 10.3389/fonc.2022.772686
236. Wang Z, Chen K, Jia Y, *et al*. Dual ARID1A/ARID1B loss leads to rapid carcinogenesis and disruptive redistribution of BAF complexes. *Nat Cancer.* 2020;1(9):909-922. doi: 10.1038/s43018-020-00109-0
237. Ding H, Quan H, Yan W, Han J. Silencing of SOX12 by shRNA suppresses migration, invasion and proliferation of breast cancer cells. *Biosci Rep.* 2016;36(5):e00389. doi: 10.1042/bsr20160053
238. Zou S, Wang C, Liu J, *et al*. Sox12 is a cancer stem-like cell marker in hepatocellular carcinoma. *Mol Cells.* 2017;40(11):847-854. doi: 10.14348/molcells.2017.0129
239. Du F, Chen J, Liu H, *et al*. SOX12 promotes colorectal cancer cell proliferation and metastasis by regulating asparagine synthesis. *Cell Death Dis.* 2019;10(3):239. doi: 10.1038/s41419-019-1481-9
240. Guo B, Xiao C, Liu Y, *et al*. miR-744-5p inhibits multiple myeloma proliferation, epithelial mesenchymal transformation and glycolysis by targeting sox12/wnt/beta-catenin signaling. *Onco Targets Ther.* 2021;14:1161-1172. doi: 10.2147/ott.s270636
241. Su Z, Bao W, Yang G, Liu J, Zhao B. SOX12 promotes thyroid cancer cell proliferation and invasion by regulating the expression of POU2F1 and POU3F1. *Yonsei Med J.* 2022;63(6):591-600. doi: 10.3349/ymj.2022.63.6.591
242. Li C, Zhu M, Zhu J, *et al*. SOX12 contributes to the activation of the JAK2/STAT3 pathway and malignant transformation of esophageal squamous cell carcinoma. *Oncol Rep.* 2021;45(1):129-138. doi: 10.3892/or.2020.7863
243. Zhang W, YuF, Weng J, *et al*. SOX12 Promotes stem cell-like phenotypes and osteosarcoma tumor growth by upregulating JAGGED1. *Stem Cells Int.* 2021;2021:9941733. doi: 10.1155/2021/9941733
244. Muratovska A, Zhou C, He S, *et al*. Paired-Box genes are frequently expressed in cancer and often required for cancer cell survival. *Oncogene.* 2003;22(39):7989-7997. doi: 10.1038/sj.onc.1206766
245. Zhong X, Li Y, Peng F, *et al*. Identification of tumorigenic retinal stem-like cells in human solid retinoblastomas. *Int J Cancer.* 2007;121(10):2125-2131. doi: 10.1002/ijc.22880
246. Mascarenhas JB, Young KP, Littlejohn EL, *et al*. PAX6 is expressed in pancreatic cancer and actively participates in cancer progression through activation of the MET tyrosine kinase receptor gene. *J Biol Chem.* 2009;284(40):27524-27532. doi: 10.1074/jbc.M109.047209
247. Li Y, Li Y, Liu Y, Xie P, Li F, Li G. PAX6, a novel target of microRNA-7, promotes cellular proliferation and invasion in human colorectal cancer cells. *Dig Dis Sci.* 2014;59(3):598-606. doi: 10.1007/s10620-013-2929-x
248. Zong X, Yang H, Yu Y, *et al*. Possible role of Pax-6 in promoting breast cancer cell proliferation and tumorigenesis. *BMB Rep.* 2011;44(9):595-600. doi: 10.5483/bmbrep.2011.44.9.595
249. Kiselev Y, Andersen S, Johannessen C, *et al*. Transcription factor PAX6 as a novel prognostic factor and putative tumour suppressor in non-small cell lung cancer. *Sci Rep.* 2018;8(1):5059. doi: 10.1038/s41598-018-23417-z
250. Wu DM, Zhang T, Liu YB, *et al*. The PAX6-ZEB2 axis promotes metastasis and cisplatin resistance in non-small cell lung cancer through PI3K/AKT signaling. *Cell Death Dis.* 2019;10(5):349. doi: 10.1038/s41419-019-1591-4
251. Zhou YH, Wu X, Tan F, *et al*. PAX6 suppresses growth of human glioblastoma cells. *J Neurooncol.* 2005;71(3):223-229. doi: 10.1007/s11060-004-1720-4
252. Shyr CR, Tsai MY, Yeh S, *et al*. Tumor suppressor PAX6 functions as androgen receptor co-repressor to inhibit prostate cancer growth. *Prostate.* 2010;70(2):190-199. doi: 10.1002/pros.21052
253. Huang BS, Luo QZ, Han Y, Li XB, Cao LJ, Wu LX. microRNA-223 promotes the growth and invasion of glioblastoma cells by targeting tumor suppressor PAX6. *Oncol Rep.* 2013;30(5):2263-2269. doi: 10.3892/or.2013.2683
254. Narbonne-Reveau K, Lanet E, Dillard C, *et al*. Neural stem cell-encoded temporal patterning delineates an early

window of malignant susceptibility in *Drosophila*. *Elife.* 2016;5:e13463.
doi: 10.7554/eLife.13463

255. Maurange C. Temporal patterning in neural progenitors: From *Drosophila* development to childhood cancers. *Dis Model Mech.* 2020;13(7):dmm044883.
doi: 10.1242/dmm.044883

256. Genovese S, Clement R, Gaultier C, *et al*. Coopted temporal patterning governs cellular hierarchy, heterogeneity and metabolism in *Drosophila* neuroblast tumors. *Elife.* 2019;8:e50375.
doi: 10.7554/eLife.50375

257. Dyson N. The regulation of E2F by pRB-family proteins. *Genes Dev.* 1998;12(15):2245-2262.
doi: 10.1101/gad.12.15.2245

258. Leone G, DeGregori J, Yan Z, *et al*. E2F3 activity is regulated during the cell cycle and is required for the induction of S phase. *Genes Dev.* 1998;12(14):2120-2130.
doi: 10.1101/gad.12.14.2120

259. Harbour JW, Luo RX, Dei Santi A, Postigo AA, Dean DC. Cdk phosphorylation triggers sequential intramolecular interactions that progressively block Rb functions as cells move through G1. *Cell.* 1999;98(6):859-869.
doi: 10.1016/s0092-8674(00)81519-6

260. Lanet E, Gould AP, Maurange C. Protection of neuronal diversity at the expense of neuronal numbers during nutrient restriction in the *Drosophila* visual system. *Cell Rep.* 2013;3(3):587-594.
doi: 10.1016/j.celrep.2013.02.006

261. Lasko P. The *drosophila* melanogaster genome: Translation factors and RNA binding proteins. *J Cell Biol.* 2000;150(2):F51-F56.
doi: 10.1083/jcb.150.2.f51

262. Liu Z, Yang CP, Sugino K, *et al*. Opposing intrinsic temporal gradients guide neural stem cell production of varied neuronal fates. *Science.* 2015;350(6258):317-320.
doi: 10.1126/science.aad1886

263. Guan W, Nie Z, Laurencon A, *et al*. The role of Imp and Syp RNA-binding proteins in precise neuronal elimination by apoptosis through the regulation of transcription factors. *Elife.* 2024;12:RP91634.
doi: 10.7554/eLife.91634

264. Ray A, Zhu H, Ding A, Li X. Transcriptional and epigenetic regulation of temporal patterning in neural progenitors. *Dev Biol.* 2022;481:116-128.
doi: 10.1016/j.ydbio.2021.10.006

265. Bley N, Schott A, Muller S, *et al*. IGF2BP1 is a targetable SRC/MAPK-dependent driver of invasive growth in ovarian cancer. *RNA Biol.* 2021;18(3):391-403.
doi: 10.1080/15476286.2020.1812894

266. Lin XT, Yu HQ, Fang L, *et al*. Elevated FBXO45 promotes liver tumorigenesis through enhancing IGF2BP1 ubiquitination and subsequent PLK1 upregulation. *Elife.* 2021;10:e70715.
doi: 10.7554/eLife.70715

267. Sperling F, Misiak D, Huttelmaier S, *et al*. IGF2BP1 promotes proliferation of neuroendocrine neoplasms by post-transcriptional enhancement of EZH2. *Cancers (Basel).* 2022;14(9):2121.
doi: 10.3390/cancers14092121

268. Chen EB, Qin X, Peng K, *et al*. HnRNPR-CCNB1/CENPF axis contributes to gastric cancer proliferation and metastasis. *Aging (Albany NY).* 2019;11(18):7473-7491.
doi: 10.18632/aging.102254

269. Li Y, Wang H, Wan J, Ma Q, Qi Y, Gu Z. The hnRNPK/A1/R/U complex regulates gene transcription and translation and is a favorable prognostic biomarker for human colorectal adenocarcinoma. *Front Oncol.* 2022;12:845931.
doi: 10.3389/fonc.2022.845931

270. Oro AE, Higgins KM, Hu Z, Bonifas JM, Epstein EH Jr, Scott MP. Basal cell carcinomas in mice overexpressing sonic hedgehog. *Science.* 1997;276(5313):817-821.
doi: 10.1126/science.276.5313.817

271. Berman DM, Karhadkar SS, Maitra A, *et al*. Widespread requirement for Hedgehog ligand stimulation in growth of digestive tract tumours. *Nature.* 2003;425(6960):846-851.
doi: 10.1038/nature01972

272. Thayer SP, Di Magliano MP, Heiser PW, *et al*. Hedgehog is an early and late mediator of pancreatic cancer tumorigenesis. *Nature.* 2003;425(6960):851-856.
doi: 10.1038/nature02009

273. Watkins DN, Berman DM, Burkholder SG, Wang B, Beachy PA, Baylin SB. Hedgehog signalling within airway epithelial progenitors and in small-cell lung cancer. *Nature.* 2003;422(6929):313-317.
doi: 10.1038/nature01493

274. Karhadkar SS, Bova GS, Abdallah N, *et al*. Hedgehog signalling in prostate regeneration, neoplasia and metastasis. *Nature.* 2004;431(7009):707-712.
doi: 10.1038/nature02962

275. Qualtrough D, Buda A, Gaffield W, *et al*. Hedgehog signalling in colorectal tumour cells: Induction of apoptosis with cyclopamine treatment. *Int J Cancer.* 2004;110(6):831-837.
doi: 10.1002/ijc.20227

276. Liao X, Siu MK, Au CW, *et al*. Aberrant activation of hedgehog signaling pathway in ovarian cancers: Effect on prognosis, cell invasion and differentiation. *Carcinogenesis.* 2009;30(1):131-140.
doi: 10.1093/carcin/bgn230

277. Hui M, Cazet A, Nair R, Watkins DN, O'Toole SA, Swarbrick A. The Hedgehog signalling pathway in breast development, carcinogenesis and cancer therapy. *Breast Cancer Res.* 2013;15(2):203.
doi: 10.1186/bcr3401

278. Jiang Y, Seimiya M, Schlumpf TB, Paro R. An intrinsic tumour eviction mechanism in *Drosophila* mediated by steroid hormone signalling. *Nat Commun.* 2018;9(1):3293.
doi: 10.1038/s41467-018-05794-1

279. Ashraf SI, Ip YT. The Snail protein family regulates neuroblast expression of inscuteable and string, genes involved in asymmetry and cell division in *Drosophila*. *Development.* 2001;128(23):4757-4767.
doi: 10.1242/dev.128.23.4757

280. Buescher M, Hing FS, Chia W. Formation of neuroblasts in the embryonic central nervous system of *Drosophila* melanogaster

is controlled by SoxNeuro. *Development.* 2002;129(18): 4193-4203.
doi: 10.1242/dev.129.18.4193

281. Rhyu MS, Jan LY, Jan YN. Asymmetric distribution of numb protein during division of the sensory organ precursor cell confers distinct fates to daughter cells. *Cell.* 1994;76(3):477-491. doi: 10.1016/0092-8674(94)90112-0
282. Doe CQ, Chu-LaGraff Q, Wright DM, Scott MP. The prospero gene specifies cell fates in the *Drosophila* central nervous system. *Cell.* 1991;65(3):451-464. doi: 10.1016/0092-8674(91)90463-9
283. Wang X, Kuang W, Ding J, *et al*. Systematic identification of the RNA-binding protein STAU2 as a key regulator of pancreatic adenocarcinoma. *Cancers (Basel).* 2022;14(15):3629. doi: 10.3390/cancers14153629
284. Wodarz A, Ramrath A, Grimm A, Knust E. *Drosophila* atypical protein kinase C associates with Bazooka and controls polarity of epithelia and neuroblasts. *J Cell Biol.* 2000;150(6):1361-1374. doi: 10.1083/jcb.150.6.1361
285. Lee CY, Robinson KJ, Doe CQ. Lgl, pins and aPKC regulate neuroblast self-renewal versus differentiation. *Nature.* 2006;439(7076):594-598. doi: 10.1038/nature04299
286. Parmentier ML, Woods D, Greig S, *et al*. Rapsynoid/partner of inscuteable controls asymmetric division of larval neuroblasts in *Drosophila*. *J Neurosci.* 2000;20(14):RC84. doi: 10.1523/JNEUROSCI.20-14-j0003.2000
287. Schaefer M, Shevchenko A, Shevchenko A, Knoblich JA. A protein complex containing Inscuteable and the Galpha-binding protein Pins orients asymmetric cell divisions in *Drosophila*. *Curr Biol.* 2000;10(7):353-362. doi: 10.1016/s0960-9822(00)00401-2
288. Han Y, Xu S, Cheng K, *et al*. CENPF promotes papillary thyroid cancer progression by mediating cell proliferation and apoptosis. *Exp Ther Med.* 2021;21(4):401. doi: 10.3892/etm.2021.9832
289. Hexiao T, Yuquan B, Lecai X, *et al*. Knockdown of CENPF inhibits the progression of lung adenocarcinoma mediated by ERbeta2/5 pathway. *Aging (Albany NY).* 2021;13(2):2604-2625. doi: 10.18632/aging.202303
290. Kanai MI, Okabe M, Hiromi Y. Seven-up Controls switching of transcription factors that specify temporal identities of *Drosophila* neuroblasts. *Dev Cell.* 2005;8(2):203-213. doi: 10.1016/j.devcel.2004.12.014
291. Sun D, Tian L, Zhu Y, *et al*. Subunits of ARID1 serve as novel biomarkers for the sensitivity to immune checkpoint inhibitors and prognosis of advanced non-small cell lung cancer. *Mol Med.* 2020;26(1):78. doi: 10.1186/s10020-020-00208-9