·Cancer Stem Cell Column·

The asymmetric division and tumorigenesis of stem cells

Qi-Zhao Wang[1], Ying-Hui Lu[1], Nan Jiang[2], Yong Diao[1], Rui-An Xu[1]

[1] Institute of Molecular Medicine, Huaqiao University, Quanzhou, Fujian 362021, P.R. China; [2] Reproductive Medicine Centre, Jiaxing Maternal and Child Health Hospital, Jiaxing, Zhejiang 314000, P.R. China

[Abstract] Stem cells use asymmetric and symmetric cell division to generate progeny. Symmetric cell division is defined as the generation of daughter cells that are destined to acquire the same fate. Stem cells divide asymmetrically to generate one daughter with a stem-cell fate and one daughter with different fate. Disruption of the machinery that regulates asymmetric division may be a reason for the generation of cancer. The asymmetric mechanism is maintained by cell polarity factors, cell fate determinants, and the spindle apparatus. The mutation or dysregulation of these factors may change stem cells from asymmetric to symmetric cell division, then leading to tumorigenesis. Therefore, further study is needed on the mechanisms of stem cell control between asymmetric and symmetric cell division, as well as the relationships among stem cells, cancer stem cells, and tumor cells. It may bring us a new approach for the resistance, recurrence, and metastasis of tumors.

Key words: Stem cell, cancer stem cell, asymmetric division, microRNA, tumorigenesis

In recent years, the hypothesis of tumor-derived cancer stem cells has received great attention. Cancer stem cells (CSCs) define a few parts of cells in tumor tissue with the characteristics of stem cells and the capacity of self-renewal, that produce daughter cells that are the same as the parent cells. In addition, with multiple differentiation potentials and highly proliferative ability, CSCs produce different phenotypes in tumor cells[1]. Studies have demonstrated that CSCs may arise from normal stem cells (NSCs) and transit-amplifying cells (TACs)[1]. Although we are uncertain whether the NSC self-control disorders lead to CSC or if TAC-retained characteristics of stem cells caused by abnormal mutation leads to CSC, or both, CSC generation needs a number of conditions, such as the mode of cell division, the cell cycle, changes in cell signaling, changes in the stem-cell microenvironment, and amplification of cells with genetic changes. Among them, dysregulation of cell division is the earliest and the most important effect on the generation of tumor cells[2-5]. Therefore, the correct understanding of the regulatory mechanisms of NSC self-renewal and differentiation will help to realize the origin, propagation, and differentiation of tumors. In this study, based on the mode of cell division, we introduce the relationship between the dysregulation of the mode of cell division and the formation of tumors.

The mode of cell division in stem cells

Stem cells maintain self-renewal and differentiation in two ways[2,6]: asymmetric cell division and symmetric cell division (Figure 1). In asymmetric cell division, stem cells divide only once and fulfill the dual needs of self-renewal and differentiation. Recently, two theories have further explained asymmetric division. One theory posits that cytoplasmic asymmetric division causes different cell fate determinants, known as intrinsic asymmetry. The other proposes that two daughter cells have the same developmental potential, yet due to different stem-cell microenvironments result in different cell fate determinants, which is known as extrinsic asymmetric division (Figure 1C). Intrinsic asymmetry can be explained by controlled theories of cell polarity factors (Figure 1A) and cell fate determinants (Figure 1B). Many processes, like growth and development, require a number of stem cells. However, according to asymmetric division, stem cells cannot proliferate, limiting the ability of embryonic development, tissue damage, and regeneration to proceed, which is a defect of asymmetric cell division. Therefore, stem cells need another mode of division to accomplish these requirements. Daughter cells produced through symmetric division have the same fate: both of the cells are either stem cells (Figure 1D) or differentiated cells (Figure 1E). The advantage of symmetric division is that the body can produce a certain type of cells in a short time. Thus, symmetric division is common in embryonic development. Evidence in adults has also proved that symmetric cell division, in

Correspondence to: Rui-An Xu; Tel: +86-595-22690952;
Email: ruianxu@hqu.edu.cn

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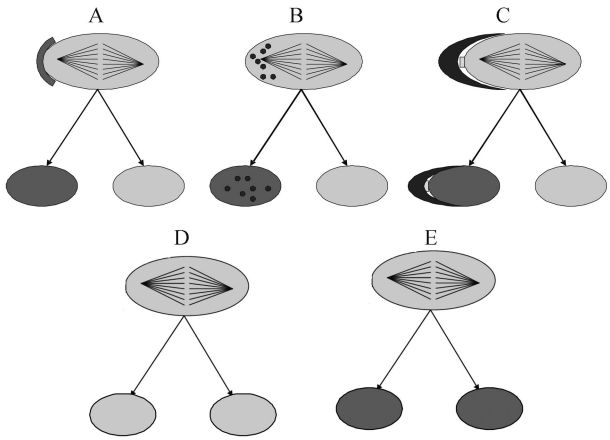

Figure 1 Asymmetric and symmetric stem-cell division

Three modes of asymmetric division: A, intrinsic asymmetric division mediated by cell polarity factors; B, intrinsic asymmetric division mediated by cell fate determinants; C, extrinsic asymmetric division. Two modes of symmetric division: D, daughter cells both have self-renewal capacities (the light green ones); E, daughter cells are both differentiated cells (the pink ones).

particular, fulfills the needs of damage and regeneration[7].

The maintenance of stem cells depends on asymmetric cell division or both asymmetric and symmetric cell division. The conversion between asymmetric and symmetric division is dually regulated by developmental and environmental signals. Some mammalian stem cells shift between asymmetric and symmetric division, according to different requirements and different stages, and the stem cells apply different modes of division. For example, in the embryonic development of both neural and epithelial stem cells, symmetric cell division is used to increase the number of stem cells. While in middle and late pregnancy, asymmetric cell division is applied to increase the variety of differentiated cells[6]. In neural stem cells, along with an increased number of differentiated cells in the forebrain, cells delaminate and stem cells divide asymmetrically to produce daughter cells. One of the daughter cells remains in the ventricular zone, and the other migrates to the overlying layer that is composed of different differentiated neurons [8]. During the formation of the stratified epidermis, asymmetric division is the dominant mode on day 14.5. One of the daughter cells remains in the basal layer, and the other migrates into the suprabasal layer and becomes a committed progenitor, which produces a limited generation of daughter cells by symmetric division before differentiation[9]. For these stem cells, defining symmetric or asymmetric division depends on whether one or two daughter cells remain in their original locations and on any stem cell related morphologic differences.

Most adult stem cells are in a resting state; only a few are active. Therefore, it is difficult to explore the division of stem cells, and the available data for in-vivo studies is very limited. In most tissues, we do not know whether asymmetric or symmetric division maintains the dynamic balance of stem cells. However, evidence has proved that some adult stem cells maintain the number of stem cells by asymmetric division at rest. In neural stem cells in the subventricular zone of the lateral ventricle, asymmetric division plays a dominant role in the steady state. However, partial symmetric division has also been observed [10]. Furthermore, a colony formation assay has shown that undifferentiated neural progenitor cells divide asymmetrically[11].

Although some adult stem cells use asymmetric division in a resting state, they can still divide symmetrically. In damage and disease situations, neural stem cells and hematopoietic stem cells use symmetric division to compensate for any reduction in the stem cell pool caused by damage. Destroyed rodent forebrain cells enhance cell division in the subventricular zone, including increasing the number of dividing cells, which, in turn, promotes neurogenesis[10]. However, the subventicular zone is composed of different cells, whether the increased cell number completely comes from stem cell division has yet to be studied. In situations of damage, hematopoietic stem cells also divide symmetrically, however, which mode they apply in the resting state we still do not understand. Chemotherapy induces damage in the hematopoietic system, and hematopoietic stem cells divide and increase the number of stem cells by symmetric division to compensate for damage caused by any depletion of the stem cell pool.

Asymmetric division of Drosophila neuroblasts

Drosophila neuroblasts (NBs) are the main materials studied in research on stem cell division[2,12]. Under normal conditions, NB has the structure of the apical-basal axis. In mitosis, messenger RNA (mRNA) and proteins are divided into apical and basal parts (Figure 2). After cell mitosis, proteins in the apical part remain in the larger cells, while proteins in the basal part enter into smaller cells. The larger daughter cells retain the capacity of self-renewal, and the smaller daughter cells become ganglion mother cells (GMCs), which can further generate pairs of neurons and pairs of neuroglial cells[13]. The differences between NB and GMC are not only reflected in the size of the cells, but also in the locations. NBs locate at the top and have contact with the neural epidermis (embryonic developmental stages) and the cortex (larval stage). GMCs and their daughter cells move to the bottom and reach the inner site of the developing central nervous system. In addition, the gene expressions in NB and GMC are different[2].

The maintenance of asymmetric cell division depends on the maintenance of cell polarity. Cell polarity regulates the asymmetric distribution of cell fate determinants and mediates the correct orientation of the spindle. Spindle orientation in turn affects cell polarity and the distribution of cell fate determinants. Thus, cell polarity factors, cell fate determinants, and the spindle affect each other and together maintain the mechanism of asymmetric division of Drosophila NB.

Baz, DmPar-6, and DaPKC compose the Par complex at the top of NBs. In the NB layered process, Insc gene is expressed. Baz is an adapter protein and binds with Insc, moving Insc anchors to the top of the NB. The Insc/Par complex constructs a crescent complex. Insc also binds with molecular chaperones Pins. Pins then binds with G protein α subunit Gαi and forms the apical complex in the NB apical cortex, which determines and

maintains the polarity of the NB and regulates the location of cell fate determinants and the orientation of the spindle. Molecules in the apical complex are dependent on each other. Functional deficiency or mutation of any one causes the failure in the formation, maintenance, and function of the apical complex (Figure 2).

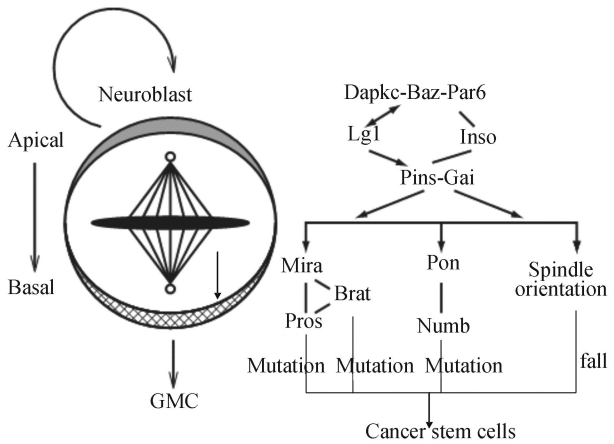

Figure 2 Drosophila neuroblast asymmetric division and cancer cell formation

Lg1, DaPKC, Baz, Par6, INSC, Pins, and Gα1 form a functional apical complex when wild-type neuroblasts divide. Apical complex formation then enables asymmetric segregation of the basal components Mira/Brat/Pros and Pon/Numb and mitotic spindle orientation, resulting in daughter cell fate determination. The bigger cell has the apical complex and keeps self-renewal capacity, while the GMC keeping cell fate determinants—Pros and Brat becomes differentiated. In GMC, Pros suppresses the transcription of key genes in the cell cycle, leading to a decrease in the biosynthesis of ribosomes and proteins. In the Brat mutated Drosophila larva, without Brat and Pros separation into GMCs, the cell cycle did not arrest, so GMCs became self-renewal cells, which keep dividing but not differentiating. Either the apical complex or mutations of cell fate determinants and spindle orientation failure could result in the formation of cancer-like cells. (Modeled after Caussinus et al., 2007[2])

Asymmetric division of NBs is controlled by an intrinsic mechanism. Cell fate determinants and adapter proteins assemble on the basal cortex of NBs before NB division, and include Mira, Pros, Brat, Numb, Pon, and so on. After NB division, these basal molecules are assigned to GMCs and determine the further differentiation of the GMCs. Mira is an adapter protein and is essential for the orientation of Pros in the basal cortex. Pros promotes GMC-specific gene expression, ends NB-specific gene expression, and is a decisive factor of asymmetric division in NBs. In GMCs, Mira is rapidly degraded and Pros enters the nucleus to regulate transcription. The tumor suppressor gene Brat also binds with Mira, and inhibits the growth of GMCs and the expression of oncogene c-Myc. Pon is also an adaptor protein and is essential for the correct distribution of Numb. The asymmetric distribution of cell fate determinants in NBs depends on apical cell polarity factors. Deficiency in apical cell polarity factors causes the fate determinant factor to fail to relocate to the bottom of the cell. The mechanisms of cell polarity factors that regulate the asymmetric division of cell fate determinants has not been discovered, except for recently in the apical complex, where three types of molecules are involved in this process, including adaptor proteins, tumor suppressor proteins (Dlg and Lgl), and myosin II and VI[2].

NBs originate from the neural epithelium. The division of epithelial cell is in the horizontal plane and the division of NBs is perpendicular to the horizontal plane, so the mitotic spindle must be rotated[12,14]. Spindle rotation is regulated by polar molecules at the top and deficiency in any molecule makes the spindle orient incorrectly[15]. Studies have shown that the relationship between spindle orientation and cell polarity is mediated by microtubules through Pins/Gαi, Dlg, and Khc73 interactions [16]. The mechanisms of polar molecules at the top regulating spindle rotation are related to the activation of the signaling pathway of the receptor-independent G protein[12,14].

Dysregulation of asymmetric division and cancer

More and more studies have suggested that the dysregulation of asymmetric stem cell division is the main reason for tumor cell formation. Transplanting NBs with gene mutations related to asymmetric division into wild-type Drosophila leads to tumorigenesis[17]. More importantly, tumors only occur in the implanted brain stem cells with mutations, but do not appear in epithelial cells with the same mutation[18]. With a simple model, Dingli *et al.*[19] proved that interfering with the asymmetric division of stem cells caused rapid proliferation of mutated stem cells, and several gene mutations could lead to this process.

Dysregulation of the asymmetric division of stem cells makes stem cells divide symmetrically, although symmetric division gives the plasticity of stem cell development, promotes cell proliferation, and enhances regeneration, while it supplies intrinsic chances for tumorigenesis. Symmetric cell division may be the precondition for tumor transformation, and tumor formation may be one of the possible ways for cells to adapt symmetric division. How does dysregulation of asymmetric division cause tumorigenesis? Cell polarity factors, mutations of the cell fate determinants, and disorders of mitotic spindle orientation that lead to tumorigenesis[2,17,20].

The abnormal functioning of DaPKC, Lg1, and Pins affect the capacity for self-renewal of NBs and leads to tumorigenesis [21]. Clones with deficiencies of Pins in NBs could form tumors[17]. Lh1 mutations in NBs produce many phenotypes in NBs, while Pins and Lg1 mutations produce a number of NBs with symmetric division[21]. Lg1 and Pins are regulated by the abnormal location of DaPKC in the cortex. Studies have shown that cell polarity plays important roles in tumor development[22]. The loss of the Drosophila cell polarity protein Scribble induces malignant results: uncontrolled cells formed and tumors generated. In mammals, knocking down Scribble in breast epithelial cells leads to the abnormal development of three-directional cellular structures, inhibits cell apoptosis, and tumors appear after a period of latency. In the pathology of mouse and human spontaneous breast cancer, not only Scribble expression reduces in patients, but also Scribble location disorders are present. Both occurring

simultaneously promote the formation of breast cancer. Molecular mechanisms show that the deficiency of Scribble increased the expression of c-Myc and that blocking the cell apoptotic pathway induces carcinogenesis.

Caussinus *et al.*[17] demonstrated that tissue with mutations of Numb, Mira, or Pros could grow to 100 times larger than normal tissue. Transplanting these cells into new hosts makes tumors recur, suggesting that these cells acheive immortality and chromosomal instability. These studies show that like the apical complex DaPKC, Lg1, and Pins, abnormal cell fate determinants also cause NB malignant transformation. Recently, two independent groups using different methods proved that Brat played roles in asymmetric division and tumorigenesis. After NB division, Brat was assigned unevenly into GMCs. Lee *et al.*[21] proved that the allelic mutation of Brat in Drosophila larvae affected the number of nerve cells in the brain. Brat mutation increased the number of daughter cells with the capacity for self-renewal and decreased the number of differentiated cells[21,23]. Betschinger *et al.*[24] considered that Brat bound with Mira, and Mira, as a cortical adaptor of cell determinant factor Pros in NBs, played a role. Both of their studies indicated that Brat bound with Mira through a Mira-binding domain and colocalized to the basal cortex of mitotic NBs. In NBs, both Brat and Pros are essential for suppressing self-renewal in one of the daughter cells. Pros regulates cell cycle related gene transcription, including cyclin A, cyclin E, and string (cdc25)[25], and Brat plays a role as a transcriptional inhibitor[23,24]. Additionally, Brat binds with RNA interaction protein through direct protein-protein interactions to inhibit specific mRNA translations[26]. Both Brat and Pros mutations cause two daughter cells to appear with NB properties and lead to the occurrence of brain tumors[23,24].

Regulatory factors that induce the asymmetric division of stem cells play conservative roles in inhibiting tumorigenesis[27]. In mammal cells, the homologous proteins of Baz, Par6, DaPKC, Lg1, and Numb have shown the ability of regulating asymmetric cell division and tumor progression. Mammalian aPKC, Par3, and LGN take part in regulating asymmetric division in epidermal progenitor cells, and the disorders of these proteins cause skin cancer[28]. Furthermore, it has been shown that asymmetric assignment of homologous Numb in vertebrates play roles as cell fate determinants[29]. Deficiencies of Numb in the mouse dorsal forebrain induce damage of neural cell differentiation, abnormal neural cells proliferation, and disrupt the cell cycle[30]. Human Lg1 and HUGL-1 homologues are also absent in tumors[31]. In mice, the absence of these genes leads to the depolarization of the central nervous system and abnormal development[32]. In breast cancer cells activated by the Notch signaling pathway, deletions of the Numb gene has been found[33]. The APC gene is necessary for the asymmetric division of Drosophila spermatogonial stem cells[24]. APC is an important tumor suppressor gene in the mammalian intestinal epithelium. Although we still do not know whether APC plays a role in regulating the mode of division of stem cells in the intestinal epithelium, except for a deficiency in the regulation of growth, other characteristics of colon tumor cells are similar to those of the intestinal epithelium[34]. All these genes inhibit tumorigenesis through many mechanisms independent of the effect of cell polarity. However, as tumor suppressors, asymmetric division may play a role in inhibiting carcinogenesis. Besides, some genes undergo symmetric division and also play roles as oncogenes in mammals. Under normal conditions, atypical protein kinase aPKC, as a part of PAR-aPKC, locates in the apical cortex of nerve cells, and specific expression of aPKC promotes symmetric cell division in NBs[21]. DaPKC has the potential of inducing tumorigenesis in Drosophila, and as an oncogene plays a role in human lung cancer cells[35]. However, AurA suppresses tumor formation by inducing aPKC asymmetric location[36]. Therefore, we speculated that in mammals, and even in humans, asymmetric division not only maintains the balance between stem cell self-renewal and differentiation, but also suppresses the formation of tumors.

Symmetric division may not only promote cell proliferation, but also may induce aneuploidy production[21]. In combination with that, the mechanism that regulates asymmetric division also mediates spindle orientation. One originator of aneuploidy induced by symmetric division is centrosomal defect, incomplete morphology, or replication errors, which finally leads to aneuploidy production at the time of chromosome division. As early as 100 years ago, Boveri proposed that centrosomes may cause tumor generation[37]. Recent studies have confirmed that abnormal centrosomes affect the chromosome division through the spindle and induced aneuploidy production[38]. In Drosophila NBs, disordered centrosomes affect the asymmetric division of cell fate determinants. Transplanting the deficient centrosomes of NBs into wild-type Drosophila induces tumorigenesis, which is consistent with cancer stem cell theory[18,39]. In mammalian cells, regulatory roles of tumor suppressor genes are very important for genetic stability. Actually, centrosomes and the spindle are tightly regulated in asymmetrically divided cells, which can ensure that daughter cells adopt different fates, while changes in spindle orientation cause tumors in Drosophila[15]. Gene mutation and aneuploidy may promote tumorigenesis through interference with the mechanism of asymmetric cell division in adult stem cells[40].

Prospects

So far, most studies about the relationship between the modes of stem cell division and the formation of tumors originate from research on Drosophila NBs. Little dysregulation of asymmetric stem cell division may induce stem cells like tumor cells and cancer stem cell production. Do the same or similar mechanisms exist in mammals (including humans)? The answer seems obvious. The existence of many malignant cancer stem cells has been proved, including cancers of the brain, lung, breast, prostate, colon, and so on. However, the relationship among stem cells, cancer stem cells, and cancer cells still needs to be validated by experimental and clinical data. In addition, how stem cells regulate the balance between symmetric and asymmetric cell division is not very clear. Most of the present

studies are based on gene mutation, however, the mutations are not reversible, and most of the mutations are transplanted artificially, which may not translate to situations in vivo. Regulating the balance between symmetric and asymmetric division should exist in other flexible and controlled ways, such as recently hot techniques, including RNAi, which is a post-transcriptional regulation mechanism. Endogenous microRNA has been found to play regulatory roles in various fields [41]. We believe that microRNA may play a role in cell division. Additionally, we should pay attention that the effect of cell polarity on cell fate may be larger than estimated. Traditional adherent cell cultures cannot simulate the complex three-directional structure in vivo, and thus are unable to study the mechanism of asymmetric division in stem cells correctly.

Theories related to asymmetric division and tumorigenesis provide new thinking for cancer therapy. Through gene modification (such as mutation and abnormally expressed genes), post-transcriptional regulation (such as siRNA and microRNA), or drugs (kinase inhibitors) to regulate the mode of stem cell division, repair damaged related genes in asymmetric cell division, or suppress the function of genes related to symmetric cell division, may inhibit tumor cell production from the origin. All of these will provide a theoretic basis and research direction for conquering tumor cell resistance, suppressing malignant tumor metastasis, and developing new drugs for recrudescent tumors.

References

[1] Wang QZ, Lv YH, Xu RA. stem cells and cancer stem cells [M]. Xu RA, Chen L, Xiao WD. Molecular Gene Medicine. Beijing: Peking University Press & Peking University Medical Press, 2008:629-675. [in Chinese]

[2] Caussinus E, Hirth F. Asymmetric stem cell division in development and cancer [J]. Prog Mol Subcell Biol, 2007,45:205-225.

[3] Furthauer M, Gonzalez-Gaitan M. Endocytosis, asymmetric cell division, stem cells and cancer: unus pro omnibus, omnes pro uno [J]. Mol Oncol, 2009, 3(4):339-353.

[4] Chang JT, Reiner SL. Asymmetric division and stem cell renewal without a permanent niche: lessons from lymphocytes [J]. Cold Spring Harb Symp Quant Biol, 2008, 73:73-79.

[5] Coumailleau F, Gonzalez-Gaitan M. From endocytosis to tumors through asymmetric cell division of stem cells [J]. Curr Opin Cell Biol, 2008, 20 (4): 462-469.

[6] Morrison SJ, Kimble J. Asymmetric and symmetric stem-cell divisions in development and cancer [J]. Nature, 2006, 441(7097):1068-1074.

[7] Eckfeldt CE, Mendenhall EM, Verfaillie CM. The molecular repertoire of the ´almighty´ stem cell [J]. Nat Rev Mol Cell Biol, 2005, 6(9):726-837.

[8] Noctor SC, Martinez-Cerdeno V, Ivic L, et al. Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases [J]. Nat Neurosci, 2004, 7(2):136-144.

[9] Lechler T, Fuchs E. Asymmetric cell divisions promote stratification and differentiation of mammalian skin [J]. Nature, 2005, 437(7056):275-280.

[10] Zhang R, Zhang Z, Zhang C, et al. Stroke transiently increases subventricular zone cell division from asymmetric to symmetric and increases neuronal differentiation in the adult rat [J]. J Neurosci, 2004, 24 (25):5810-5815.

[11] Zhang F, Yan Q, Yan W, et al. Cancer is a disease of unregulated expansion of somatic stem cells resulting from disrupted asymmetric division [J]. Med Hypothesis, 2008, 70(1):208-289.

[12] Wu PS, Egger B, Brand AH. Asymmetric stem cell division: lessons from Drosophila [J]. Semin Cell Dev Biol, 2008, 19(3):283-293.

[13] Wodarz A, Huttner WB. Asymmetric cell division during neurogenesis in Drosophila and vertebrates [J]. Mech Dev, 2003, 120(11):1297-1309.

[14] Egger B, Boone JQ, Stevens NR, et al. Regulation of spindle orientation and neural stem cell fate in the Drosophila optic lobe [J]. Neural Dev, 2007, 2(1):1-14.

[15] Gonzalez, C. Spindle orientation, asymmetric division and tumour suppression in Drosophila stem cells [J]. Nat Rev Genet, 2007, 8(6): 462-472.

[16] Siegrist SE, Doe CQ. Microtubule-induced Pins/Galphai cortical polarity in Drosophila neuroblasts [J]. Cell, 2005, 123(7):1323-1335.

[17] Caussinus E, Gonzalez C. Induction of tumor growth by altered stem-cell asymmetric division in Drosophila melanogaster [J]. Nat Genet, 2005, 37 (10):1125-1129.

[18] Castellanos E, Dominguez P, Gonzalez C. Centrosome dysfunction in Drosophila neural stem cells causes tumors that are not due to genome instability [J]. Curr Biol, 2008, 18 (16):1209-1214.

[19] Dingli D, Traulsen A, Michor F. (A) Symmetric stem cell replication and cancer [J]. PLoS Comput Biol, 2007, 3(3): e53.

[20] Doe CQ, Bowerman B. Asymmetric cell division: fly neuroblast meets worm zygote [J]. Curr Opin Cell Biol, 2001, 13(1):68-75.

[21] Lee CY, Robinson KJ, Doe CQ. Lgl, Pins and aPKC regulate neuroblast self-renewal versus differentiation [J]. Nature, 2006, 439(7076):594-598.

[22] Zhan L, Rosenberg A, Bergami KC, et al. Deregulation of scribble promotes mammary tumorigenesis and reveals a role for cell polarity in carcinoma [J]. Cell, 2008, 135(5):865-878.

[23] Lee CY, Wilkinson BD, Siegrist SE, et al. Brat is a Miranda cargo protein that promotes neuronal differentiation and inhibits neuroblast self-renewal [J]. Dev Cell, 2006, 10(4):441-449.

[24] Betschinger J, Mechtler K, Knoblich JA. Asymmetric segregation of the tumor suppressor brat regulates self-renewal in Drosophila neural stem cells [J]. Cell, 2006, 124(6):1241-153.

[25] Li L, Vaessin H. Pan-neural Prospero terminates cell proliferation during Drosophila neurogenesis [J]. Genes Dev, 2000, 14(2):147-151.

[26] Sonoda J, Wharton RP. Drosophila brain tumor is a translational repressor [J]. Genes Dev, 2001, 15(6):762-773.

[27] Humbert P, Russell S, Richardson H. Dlg, Scribble and Lgl in cell polarity, cell proliferation and cancer [J]. BioEssays, 2003, 25 (6): 542-553.

[28] Lechler T, Fuchs E. Asymmetric cell divisions promote stratification and differentiation of mammalian skin [J]. Nature, 2005, 437(7056):2752-80.

[29] Wodarz A, Huttner WB. Asymmetric cell division during neurogenesis of Drosophila and vertebrates [J]. Mech Dev, 2003, 120(11):1297-1309.

[30] Li HS, Wang D, Shen Q, S et al. Inactivation of numb and numblike in embryonic dorsal forebrain impairs neurogenesis and disrupts cortical morphogenesis [J]. Neuron, 2003, 40(6):1105-1118.

[31] Kuphal S, Wallner S, Schimanski CC, et al. Expression of Hugl-1 is strongly reduced in malignant melanoma [J]. Oncogene, 2006, 25(1): 103-110.

[32] Klezovitch O, Fernandez TE, Tapscott SJ, et al. Loss of cell polarity causes severe brain dysplasia in lgl1 knockout mice [J]. Genes Dev, 2004, 18(5):559-571.

[33] Regala RP, Weems C, Jamieson L, et al. Atypical protein kinase C iota is an oncogene in human non-small cell lung cancer [J]. Cancer Res, 2005, 65(9): 8905-8911.

[34] Yamashita YM, Jones DL, Fuller MT. Orientation of asymmetric stem cell division by the APC tumor suppressor and centrosome [J]. Science, 2003, 301(5639):1547-1550.

[35] Zhang JW, Niu C, Ye L, et al. Identification of the haematopoietic stem cell niche and control of the niche size [J]. Nature, 2003, 425(6960): 836-841.

[36] Wang H, Somers GW, Bashirullah A, et al. Aurora-A acts as a tumor suppressor and regulates self-renewal of Drosophila neuroblasts [J]. Genes Dev, 2006, 20(24):3453-3463.

[37] Boveri T. Concerning the origin of malignant tumours by theodor boveri.

translated and annotated by benry Harris [J]. J Cell Sci, 2008,121(Suppl 1):1–84.

[38] Ganem NJ, Godinho SA, Pellman D. A mechanism linking extra centrosomes to chromosomal instability [J]. Nature, 2009, 460(7252):278–282.

[39] Basto R, Brunk K, Vinadogrova T, et al. Centrosome amplification can initiate tumorigenesis in flies [J]. Cell, 2008, 133(6):1032–1042.

[40] Zhang F, Zhao D, Chen G, et al. Gene mutation and aneuploidy might cooperate to carcinogenesis by dysregulation of asymmetric division of adult stem cells [J]. Med Hypotheses, 2006, 67(4):995–996.

[41] Wang Q, Xu W, Habib N, et al. Potential uses of miRNA in lung cancer diagnosis, prognosis, and therapy [J]. Curr cancer drug targets, 2009, 9 (4):572–594.