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Asymmetric and symmetric stem-cell divisions in development and cancer

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Much has been made of the idea that asymmetric cell division is a defining characteristic of stem cells that enables them to simultaneously perpetuate themselves (self-renew) and generate differentiated progeny. Yet many stem cells can divide symmetrically, particularly when they are expanding in number during development or after injury. Thus, asymmetric division is not necessary for stem-cell identity but rather is a tool that stem cells can use to maintain appropriate numbers of progeny. The facultative use of symmetric or asymmetric divisions by stem cells may be a key adaptation that is crucial for adult regenerative capacity.

Stem cells are defined by both their ability to make more stem cells, a property known as 'self-renewal', and their ability to produce cells that differentiate (Fig. 1a). One strategy by which stem cells can accomplish these two tasks is asymmetric cell division, whereby each stem cell divides to generate one daughter with a stem-cell fate (self-renewal) and one daughter that differentiates[1–4] (Fig. 1b). Asymmetric division is a particularly attractive strategy because it manages both tasks with a single division; however, a disadvantage of this strategy is that it leaves stem cells unable to expand in number. This lack of flexibility is a problem, given that stem-cell numbers can increase markedly, both when stem-cell pools are first established during development[5–7] and when they are regenerated after injury[8–11]. Thus, asymmetric cell divisions cannot be the complete story. Stem cells must have additional self-renewal strategies that permit dynamic control of their numbers.

Stem cells can also use symmetric divisions to self-renew and to generate differentiated progeny. Symmetric divisions are defined as the generation of daughter cells that are destined to acquire the same fate. Although the idea that stem cells can divide symmetrically may seem counterintuitive, stem cells are defined by their 'potential' to generate more stem cells and differentiated daughters, rather than by their production of a stem cell and a differentiated daughter at each division. When viewed as a population, a pool of stem cells with equivalent developmental potential may produce only stem-cell daughters in some divisions and only differentiated daughters in others. In principle, stem cells can rely either completely on symmetric divisions (Fig. 1c) or on a combination of symmetric and asymmetric divisions (Fig. 1d). The evidence for symmetric stem-cell divisions is strong, both in model organisms such as *Caenorhabditis elegans* and *Drosophila*, and in vertebrates.

In this review, we explore the idea that most stem cells can divide by either asymmetric or symmetric modes of division, and that the balance between these two modes is controlled by developmental and environmental signals to produce appropriate numbers of stem cells and differentiated daughters. In this review, we define a cell division as asymmetric or symmetric according to the fates of its daughter cells. Available data, although often incomplete, suggest that most stem cells have the ability to switch between asymmetric and symmetric modes of division, and that the balance between these two modes of division is defective in some disease states.

Stem cells and asymmetric cell division

The roles of asymmetric cell division in stem-cell control, coupled with the mechanisms that regulate this process, have been extensively reviewed[1–4]. In brief, two main types of mechanism govern asymmetric cell divisions. The first relies on the asymmetric partitioning of cell components that determine cell fate; we refer to such mechanisms as 'intrinsic'. The second involves the asymmetric placement of daughter cells relative to external cues; we refer to these mechanisms as 'extrinsic'.

Intrinsic mechanisms include regulated assembly of cell polarity factors (Fig. 2a) and regulated segregation of cell fate determinants (Fig. 2b). In situations in which the only difference between the daughter cells is their position relative to the stem-cell niche (Fig. 2c), the daughter cells may initially have equivalent developmental potential, but they may acquire different fates owing to exposure to varying external signals. In this way, the division is asymmetric with respect to the ultimate fate of the daughter cells even though the division is intrinsically symmetric, initially yielding two daughter cells with equivalent developmental potential. For many asymmetric divisions, the mitotic spindle is regulated so that its orientation is reproducible — a process that can be controlled by both extrinsic and intrinsic cues.

A classic example of an asymmetric division that is controlled by an intrinsic mechanism is provided by the *C. elegans* zygote, which divides asymmetrically to produce one larger blastomere fated to make ectoderm, and one smaller blastomere that produces mesoderm, endoderm and finally germ line in a series of asymmetric divisions[3]. Although not a traditional stem cell, this early embryonic lineage provides a model for asymmetric stem-cell divisions because each division produces one daughter cell that will produce only somatic cells and a second daughter cell that is capable of generating germ line. Furthermore, these embryonic divisions rely on mechanisms that are widely used by asymmetrically dividing stem cells and progenitors.

Asymmetric division of *C. elegans* zygotes requires asymmetric localization of the PAR-3, PAR-6 and atypical protein kinase C (PAR–aPKC) complex at the cortex (Fig. 2a; and reviewed in ref. 12). The asymmetrically localized PAR proteins in turn govern both mitotic spindle orientation and asymmetric segregation of cytoplasmic cell fate determinants, including riboprotein particles known as P granules and PIE-1, a transcriptional repressor required for germline fate[12–16] (Fig. 2b).

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Asymmetric division of the *Drosophila* neuroblast is controlled by a closely related mechanism[3,17]. Moreover, in *Drosophila* neuroblasts, an evolutionarily conserved cell fate determinant, Numb, is asymmetrically localized to daughter cells that are destined to differentiate[18].

A classic example of an asymmetric division that is controlled by an extrinsic mechanism is provided by the *Drosophila* germline stem cell, which divides with a reproducible orientation to generate one daughter that remains in the stem-cell niche and retains stem-cell identity, and one daughter that is placed away from the niche and begins to differentiate[4,19,20]. A stem-cell niche is defined as a 'microenvironment' that promotes stem-cell maintenance (refs 21, 22; see also page 1075). Cells that create stem-cell niches include cap cells in the *Drosophila* ovary[19] and hub cells in the *Drosophila* testis[23,24]. In the ovary, cap cells synthesize ligands called Decapentaplegic (DPP) and Glass bottom boat (GBB) that activate bone morphogenetic protein (BMP) signalling in germline stem cells, thereby repressing the gene *bag-of-marbles*[25,26], which encodes a protein that promotes differentiation[27]. In the testis, hub cells synthesize a ligand called Unpaired that activates the JAK–STAT (Janus kinase and signal transducer and activator of transcription) signalling pathway in germline stem cells to prevent differentiation, presumably by controlling target genes that remain to be identified[4,23,24]. Specialized junctions at the interface between the niche and germline stem cells anchor the stem cell to the niche[28,29]. The mechanism controlling orientation of the mitotic spindle relies on centrosomal components in spermatogonial stem cells[29]. More importantly for our discussion here, the orientation of these asymmetric stem-cell divisions controls the location of daughter cells and thus their access to extrinsic signals that regulate stem-cell identity.

It is important to note that asymmetric divisions can be governed by both intrinsic partitioning of fate regulators and asymmetric exposure to extrinsic cues. Sperm entry initiates asymmetry of the *C. elegans* zygote[30,31], and signalling from the neural epithelium orients divisions of *Drosophila* neuroblasts[32] (Fig. 2c). Furthermore, Numb modifies the response to Notch signalling of the daughter cell that inherits it, indicating that cell fate determinants can function by altering the response to external cues[33]. By contrast, asymmetric division of *Drosophila* germline stem cells does not seem to rely on partitioning of cell fate determinants. Although each germline stem cell is marked by a cytoplasmic organelle called the 'spectrosome', the function of this asymmetrically distributed organelle remains uncertain. In addition, daughters of the germline stem-cell division seem to be equivalent in developmental potential, as we discuss below. Thus, these divisions seem to be intrinsically symmetric in terms of developmental potential, but seem to achieve an asymmetric outcome through the distinct positions of the daughter cells relative to the niche.

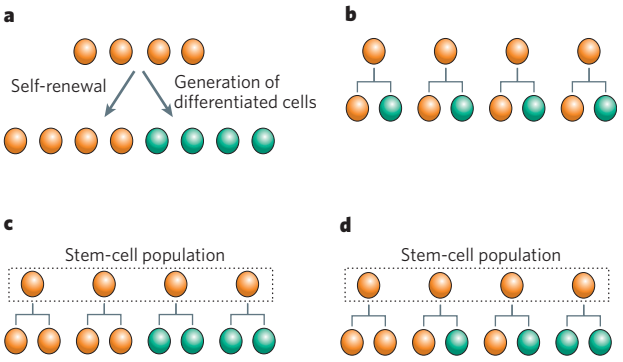

Figure 1 | Stem-cell strategies. **a,** Stem cells (orange) must accomplish the dual task of self-renewal and generation of differentiated cells (green). **b–d,** Possible stem-cell strategies that maintain a balance of stem cells and differentiated progeny. **b,** Asymmetric cell division: each stem cell generates one daughter stem cell and one daughter destined to differentiate. **c, d,** Population strategies. A population strategy provides dynamic control over the balance between stem cells and differentiated cells — a capacity that is necessary for repair after injury or disease. In this scheme, stem cells are defined by their 'potential' to generate both stem cells and differentiated daughters, rather than their actual production of a stem cell and a differentiated cell at each division. **c,** Symmetric cell division: each stem cell can divide symmetrically to generate either two daughter stem cells or two differentiated cells. **d,** Combination of cell divisions: each stem cell can divide either symmetrically or asymmetrically.

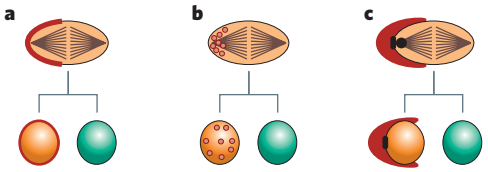

Figure 2 | Controls of asymmetric stem-cell division. Three simple mechanisms are shown, but others are plausible. For molecular details, see recent reviews[1–4,12,17,31]. **a,** Asymmetric localization of cell polarity regulators (red) initiates the asymmetric division. Shown is asymmetric assembly of the PAR–aPKC complex at one end of the dividing cell. Stem cells are orange, differentiated cells are green. **b,** Cell fate determinants (red) can be segregated to the cytoplasm of one daughter cell, as shown here, or they can be associated with the membrane, centrosome or another cellular constituent that is differentially distributed to the daughters. **c,** Regulated orientation of the mitotic spindle retains only one daughter in the stem-cell niche (red), such that only that daughter cell has access to extrinsic signals necessary for maintaining stem-cell identity. This mechanism achieves an asymmetric outcome, even though the division itself is intrinsically symmetric. In an alternative but similar model, the daughter cell placed away from the niche is exposed to signals that induce differentiation.

Some mammalian stem-cell divisions possess hallmarks of asymmetry and seem to be controlled by evolutionarily conserved mechanisms. An example is the division of neural progenitors. Undifferentiated neural progenitors in the developing rodent cortex distribute Numb asymmetrically to precursors destined for neurogenesis[34–36]. The inhibition of Notch signalling by Numb is crucial for neurogenesis in flies, and it also seems to be involved in the regulation of mammalian asymmetric division[33,37,38]. Numb is also asymmetrically distributed to progeny of cultured satellite muscle cells, where it promotes myogenic differentiation of one daughter cell[39]. Thus, asymmetric segregation of Numb may be a common mode of control. A second example is the regulated orientation of mitotic spindles, which has been found in both mammalian basal epidermal progenitors[7] and cortical ventricular zone neural progenitors[40]. Indeed, spindle orientation relies on the cortical localization of the conserved PAR–aPKC complex[7], a mechanism that also controls the asymmetric division of *Drosophila* neuroblasts[41,42]. Thus, mammalian progenitors are likely to use some of the mechanisms of invertebrate progenitors to divide asymmetrically.

Symmetric divisions can expand stem-cell number

Symmetric stem-cell divisions have been observed during the development of both invertebrates and vertebrates. Symmetric stem-cell divisions are also common during wound healing and regeneration. A hallmark of all three processes is an increase in the number of stem cells. This increase cannot be explained by a strategy restricted to asymmetric cell division in which only one daughter cell maintains stem-cell identity.

A classic example of symmetric stem-cell division during development occurs in the *C. elegans* germ line. The larval nematode hatches from its eggshell with only two germline stem cells but, during subsequent larval development, these germ cells proliferate to produce roughly 2,000 descendants in the adult gonad, including one pool of undifferentiated germ cells and another pool of differentiating gametes[5,43] (Fig. 3a). During larval development and in adults, *C. elegans* germline stem cells are maintained by signalling from a niche formed by the 'distal tip cell'[5]. In contrast to the *Drosophila* niches, which rely on BMP and JAK–STAT signalling[23,24,44,45], the distal tip cell niche uses Notch signalling to control *C. elegans* germline stem cells throughout development and in adults[43].

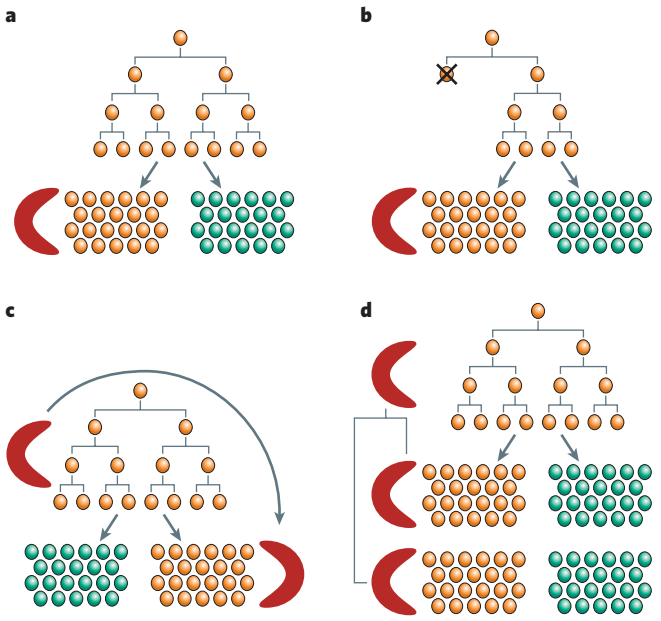

Figure 3 | Symmetric divisions in the developing *C. elegans* germ line. **a,** *C. elegans* germline divisions during development are symmetric with respect to size and morphology of daughter cells, cleavage plane and position[46]. Continued mitotic divisions rely on signalling from the stem-cell niche[5,46,87]. Stem cells are orange; differentiated cells are green; the stem-cell niche is red. **b,** Elimination of one or more germ cells by laser ablation (marked with a cross) during early (shown) or later larval development does not affect the ability to generate pools of stem cells and differentiated cells[5]. Mitotic germ cells are therefore developmentally equivalent. **c,** Repositioning the niche induces germline stem cells at the new position[5]. **d,** Niche duplication results in duplication of the germline stem-cell pool. Niche duplication has been accomplished by alterations in either the cell-cycle machinery[47,48,50] or regulators of niche specification[49,51].

Several lines of evidence show that *C. elegans* germ cells divide symmetrically during larval development. First, these divisions produce daughters of equal size and morphology, and they are variable with respect to both plane of cleavage and daughter cell position[46]. Second, one or more germ cells can be removed by laser ablation without eliminating the capacity of the stem cells for both self-renewal and generation of gametes[5] (Fig. 3b). Third, experimental repositioning of the stem-cell niche during early development — a time when all germ cells are proliferating — results in maintenance of the stem-cell fate by whatever germ cells happen to be located near the new niche position[5] (Fig. 3c). Last, duplication of the niche results in duplication of germline stem-cell pools[47–51] (Fig. 3d). Thus, during the expansion phase of germline development, *C. elegans* germ cells generate daughters with equivalent developmental potential, and these daughter cells ultimately acquire distinct fates depending on the position and number of niche cells. A similar phenomenon of symmetric germ cell divisions during larval development has recently been documented in *Drosophila*[52].

Mammalian stem cells also seem to undergo largely symmetric divisions to expand stem-cell pools during embryonic or early fetal development. For example, mouse haematopoietic stem (HS) cells double in number every day during mid-gestation[6], implying that a substantial fraction of these stem cells must undergo symmetric self-renewing divisions. However, direct imaging of these stem-cell divisions has not been possible. By contrast, it has been possible to image both the divisions of undifferentiated neural progenitors in cultured slices of the developing rodent cerebral cortex[40,53,54] and cell divisions in the basal layer of the fetal epidermis[7]. During embryonic development of the cerebral cortex and epidermis, the pool of undifferentiated progenitors initially expands in number before significant amounts of differentiated cells are generated. During this expansion, cell divisions in the cortical ventricular zone generate two morphologically identical daughter cells that seem to be undifferentiated and lie side by side in the ventricular zone where stem cells are located. Similarly, cell divisions in the fetal epidermis seem to be largely symmetric, generating morphologically equivalent undifferentiated cells in the plane of the basal layer of the epidermis where stem cells are present[7]. It remains formally possible, however, that morphologically and positionally equivalent progeny in locations known to contain stem cells could have different developmental potentials. Thus, without direct information on developmental potential or fate, inferences regarding symmetric versus asymmetric divisions of stem cells are based on incomplete criteria and should be considered provisional.

Symmetric divisions can persist into adulthood

Symmetric stem-cell divisions are common in developing tissues, but they can also be observed in adults, as exemplified by the adult *Drosophila* ovary. As described above, adult *Drosophila* germline stem cells normally divide asymmetrically[55] (Fig. 4a); however, female germline stem cells can be induced to divide symmetrically and to regenerate an additional stem cell after an experimental manipulation in which one stem cell is removed from the niche (Fig 4b). Thus, adult *Drosophila* germline stem cells are regulated to divide asymmetrically or symmetrically.

Recent experiments further suggest that the daughters of *Drosophila* germline stem cells have equivalent developmental potential despite their distinct cellular morphologies (Fig. 4c). In these experiments, germline stem cells were induced to differentiate by altering specific regulators: in the ovary, the *bag-of-marbles* activator of differentiation was ectopically expressed by using a heat shock promoter[52]; in the testis, the *stat92E* stem-cell activator was depleted by using a temperature-sensitive mutant[56]. The former experiment also required ectopic expression of the DPP ligand in somatic ovarian cells. In both studies, germline stem cells located in the niche lost their stem-cell morphology and adopted cellular characteristics of a daughter fated to differentiate (Fig. 4c). When the activities of the regulators were reversed, however, the differentiating cells reverted to a stem-cell morphology and resumed a stem-cell fate.

The simplest explanation is that asymmetric divisions of *Drosophila* germline stem cells produce daughters of equivalent potential but place them in different positions with respect to signalling from the niche (Fig. 4d). These equivalent daughters then adopt distinct identities depending on the presence or absence of signalling from the niche (Fig. 4d). This idea could have been tested more directly, either by reversing the positions of the two daughter cells with respect to the niche to see whether their fates could be reversed, or by removing the stem cell by laser ablation to determine whether its differentiating sister could enter the niche and adopt the stem-cell fate. However, such physical manipulations are technically challenging in this system.

Symmetric stem-cell divisions are also common in the adult *C. elegans* germ line. Although individual germline stem cells in the adult gonad have not been identified by lineage tracing, a region of mitotically dividing germ cells called the 'mitotic region' is responsible for both self-renewal and replenishment of germ cells[57,58] (Fig. 4e). Unlike *Drosophila* germline stem-cell divisions, which are reproducibly oriented with respect to the niche[29,55], *C. elegans* germ cells do not divide along any particular axis[58] (Fig. 4f, g). Indeed, about one-fifth of the germline stem-cell divisions maintain both daughters in the niche (Fig. 4e), whereas the other four-fifths place daughter cells in variable positions with respect to the niche (Fig. 4f).

A key unresolved issue is whether *C. elegans* germline stem cells divide asymmetrically with respect to their developmental potential. However, given the symmetric germline divisions in the early larval *C. elegans* germ line[5,46], and evidence that *Drosophila* germline stem-cell daughters are equivalent in developmental potential[52,56], it seems likely that adult *C. elegans* germline stem-cell divisions are also symmetric, and that differentiation results in daughters that become displaced from the niche. Consistent with this idea, molecular regulators promoting the differentiated state are expressed in germline daughter cells located outside the niche at a point about halfway through the mitotic region[59,60] (Fig. 4e).

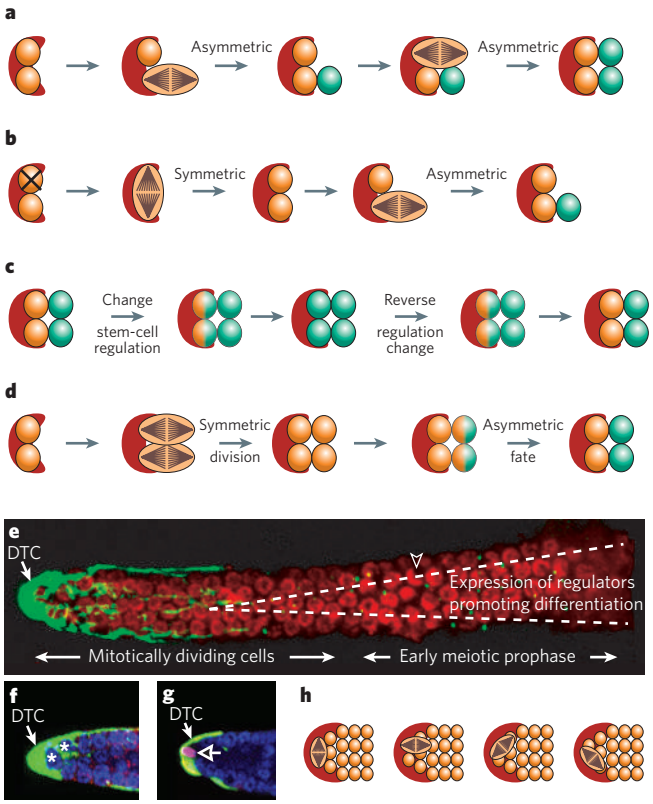

Figure 4 | Symmetric stem-cell divisions in the adult germ line. a–d, Adult *Drosophila* germline stem cells. **a,** Germline stem-cell divisions in the ovary are normally asymmetric. The niche (red) contains 2–3 germline stem cells (orange). Each divides with a mitotic spindle oriented toward the niche, retaining one daughter in the niche and placing the other outside the niche (green). **b,** Elimination of one germline stem cell (marked with a cross) leads to symmetric stem-cell division of the other germline stem cell[19]. **c,** Daughters of germline stem-cell division have equivalent developmental potential: germline stem cells in the niche can be induced to express cellular markers of differentiation (green) by manipulating stem-cell regulators[52,56]. When this manipulation is reversed, the cells revert to a stem-cell fate. **d,** The experiments shown in **c** suggest that germline stem cells produce daughters with equivalent developmental potential, but the daughter outside the niche gradually changes into a differentiated state (graded orange to green). In this way, the oriented divisions yield daughters that acquire different fates despite initially having the same potential. **e–h,** Adult *C. elegans* germline stem cells. **e,** Germline stem cells in the adult gonad. The distal tip cell (DTC), shown expressing green fluorescent protein (green), provides a stem-cell niche for germ cells[5] (red). The mitotic region includes ~225 germ cells; germline nuclei in early meiotic prophase are crescent-shaped (arrowhead). *gld-1* mRNA and protein products, which promote differentiation[88], are undetectable in germ cells close to the niche, but become detectable about half way through the mitotic region and are at higher concentrations (broken lines) as germ cells enter meiotic prophase[59]. (Image adapted, with permission, from *WormBook*[43] and courtesy of S. Crittenden, Howard Hughes Medical Institute, Wisconsin, USA, and J.K.) **f,** The niche extends short processes that almost surround the distal-most germ cells (asterisks). These short processes may anchor the germ cells in the niche[58]. (Image courtesy of S. Crittenden.) **g,** Approximately 20% of germ cells lying in the niche divide with an orientation that retains both daughters in the niche[58] (metaphase plate, pink). (Image courtesy of S. Crittenden.) **h,** The orientations of germline stem-cell mitotic spindles are not fixed[58].

Symmetric and asymmetric divisions of mammalian stem cells

Some mammalian stem cells seem to switch between symmetric and asymmetric cell divisions. For example, both neural and epidermal progenitors change from primarily symmetric divisions that expand stem-cell pools during embryonic development (Fig. 5a, c) to primarily asymmetric divisions that expand differentiated cell numbers in mid to late gestation (Fig. 5b). For these cells, divisions are classified as symmetric or asymmetric depending on whether one or both daughter cells retain the position and morphology associated with stem cells.

As layers of differentiated cells arise in the forebrain, progenitors increasingly undergo apparently asymmetric divisions: one cell remains in the ventricular zone (where stem cells are located) and the other cell migrates into overlying layers of differentiated neurons[40,53]. During formation of a stratified epidermis, asymmetric divisions begin to predominate at embryonic day 14.5 and lead to the generation of one cell that remains in the basal layer (where stem cells are located) and a second cell that migrates into a suprabasal layer of committed progenitors that are fated to undergo a limited number of symmetric divisions before differentiating[7,61]. Thus, these mammalian stem cells seem to make a developmentally regulated transition from largely symmetric to predominantly asymmetric divisions during mid to late gestation. A caveat, however, is that mammalian stem cells cannot be distinguished from other progenitors on the basis of only morphology and position, so it remains possible that the frequency of asymmetric and symmetric divisions of stem cells differs from that observed in the overall pool of undifferentiated cells.

Only limited data are available on the modes of division used by adult mammalian stem cells *in vivo*. Adult mammalian stem cells are quiescent most of the time[62,63], and the rarity of adult stem-cell divisions makes them technically difficult to image. In most tissues, it is not known whether homeostasis is maintained by asymmetric divisions (Fig. 1b), or by a population strategy that uses symmetric divisions to balance stem cells and differentiated progeny (Fig. 1c, d). Nonetheless, evidence is starting to indicate that at least some adult stem cells divide asymmetrically under steady-state conditions to maintain population size (Fig. 5d). In the subventricular zone of the adult forebrain, for example, asymmetric divisions predominate under steady-state conditions, although some apparently symmetric divisions can be observed[64]. Furthermore, clonal analyses based on retroviral marking of individual progenitors support the idea that undifferentiated neural progenitors divide asymmetrically[65,66]. Homeostasis is also maintained in the adult oesophagus by apparently asymmetric cell divisions of progenitors in the basal layer[61].

Although some adult stem cells seem to divide asymmetrically under steady-state conditions, they retain the capacity to divide symmetrically to restore stem-cell pools depleted by injury or disease (Fig. 5e), as has been observed in the nervous and haematopoietic systems. In the mouse forebrain, the frequency of subventricular zone cells capable of forming neural stem-cell colonies in culture is markedly reduced after infusion of an antimitotic drug. Neural stem cells begin dividing soon after the infusion, however, and within days they restore a normal frequency of cells that can form neural stem-cell colonies in culture[11]. HS cells also divide symmetrically after injury, although it is not known whether they divide asymmetrically or symmetrically under steady-state conditions. In any event, when the haematopoietic system is decimated by chemotherapy, HS cells begin dividing and expand about tenfold in number to regenerate pools of both stem cells and differentiated cells[8–10]. The common theme is that stem cells adopt a symmetric mode of division to regenerate depleted stem-cell pools after injury.

In mammals, symmetric divisions also increase in number after more physiological injuries. The death of rodent forebrain cells after stroke increases the rate of division among subventricular zone progenitors, including a rise in symmetric cell divisions that, in turn, leads to an increase in neurogenesis[64]. These data are consistent with the above examples of stem cells that divide symmetrically to replace cells lost through injury. Subventricular zone progenitors, however, are heterogeneous and include both stem cells and other types of progenitor[67,68]. So far there is no evidence for an increase in the absolute number of cells with stem-cell function in stroke; thus, it remains possible that the observed symmetric divisions occurred in transit-amplifying cells or restricted progenitors, rather than in stem cells. As new markers are discovered that rigorously identify mammalian stem cells *in vivo* and can distinguish these cells from intrinsically different populations of transit-amplifying cells, it will be possible to refine our understanding of mammalian stem-cell behaviour in the niche[69].

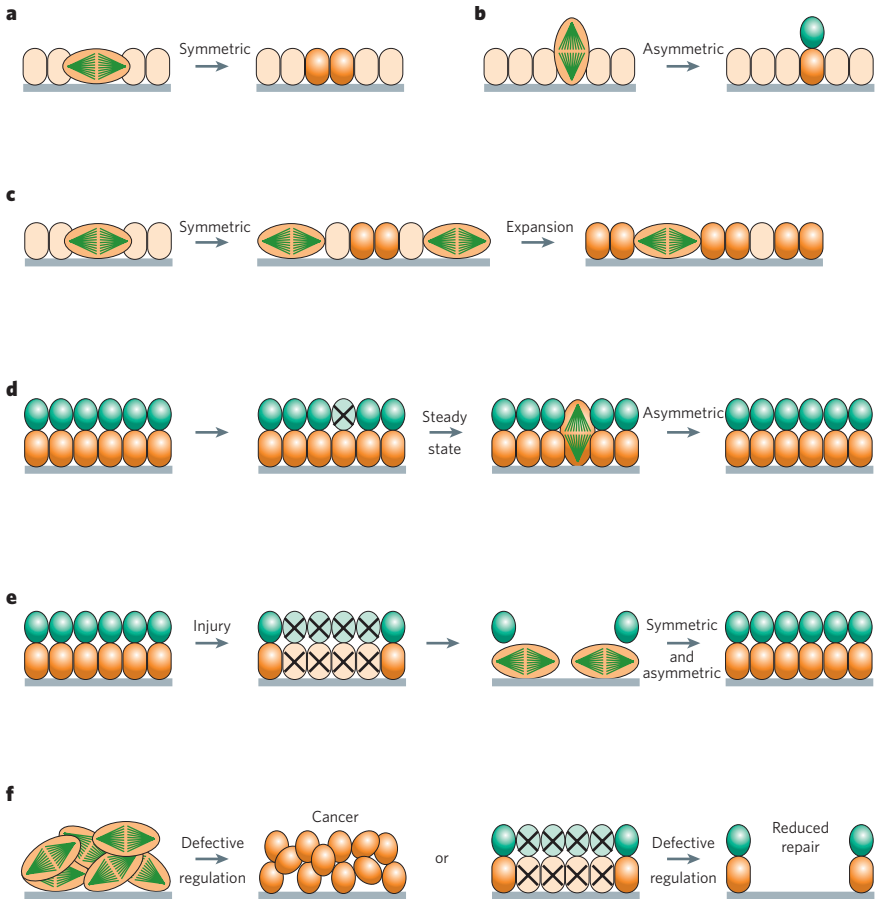

Figure 5 | Stem cells can facultatively use both symmetric and asymmetric divisions. **a,** Division in the plane of the epithelium generates two morphologically similar daughter cells that are both likely to be stem cells (orange). Grey line, basement membrane. **b,** Division perpendicular to the plane of the epithelium generates one stem cell and one differentiated daughter (green). Such asymmetric divisions by stem cells are thought to predominate during late fetal development and adulthood in the basal layer of epithelia[7,61] and in the ventricular zone of the brain[40,53]. Although spindle orientation seems to correlate with cell fate in this manner in various systems, it is not an obligate relationship because current data on progenitor identity and daughter cell fates are incomplete, and divisions in the plane of the epithelium can sometimes yield progenitors that acquire different fates[54]. **c,** During development, symmetric divisions expand the stem-cell pool. **d,** In healthy adults, divisions perpendicular to the epithelial plane typically maintain normal numbers of stem cells and differentiated cells in the basal layer of epithelia and in the subventricular zone of the brain. **e,** In healthy adults, cells can be lost to injury (X). Symmetric divisions are proposed to regenerate additional stem cells, and asymmetric divisions to regenerate differentiated daughters. **f,** We speculate that defects in regulation of the switch between symmetric and asymmetric divisions can be deleterious. Left, a defect favouring symmetric divisions results in tumorigenesis. Right, a defect favouring asymmetric divisions results in decreased capacity for tissue repair. Both tumorigenesis and poor wound healing are typical of ageing animals, raising the question of whether defects in switch mechanisms accumulate with age.

Stem-cell divisions and cancer

The capacity for symmetric stem-cell self-renewal may confer developmental plasticity, increased growth and enhanced regenerative capacity; however, it may also confer an inherent risk of cancer. Normally, *Drosophila* neuroblasts divide asymmetrically[3] as a result of the asymmetric localization of cortical cell polarity determinants (such as Partner of Inscuteable (PINS) and aPKC) and cell fate determinants (for example, Numb and Prospero), and regulated alignment of the mitotic spindle (Fig. 2). When the machinery that regulates asymmetric divisions is disrupted, however, these neuroblasts begin dividing symmetrically and form tumours[42,70,71].

Cell clones lacking PINS are tumorigenic[42,71], and double mutant cells lacking both PINS and Lethal giant larvae (LGL) generate a brain composed largely of symmetrically dividing and self-renewing neuroblasts[42]. Cell clones lacking the cell fate determinants Numb or Prospero are tumorigenic and can be propagated after transplantation into new hosts[71]. Moreover, these tumour cells have been shown to become aneuploid within 40 days of adopting a symmetric mode of division[71]. This finding indicates that invertebrate cells are capable of rapid neoplastic transformation. An intriguing possibility is that the capacity to divide symmetrically may be a prerequisite for neoplastic transformation and that cancer may reflect, at least in part, the capacity to adopt a symmetric mode of cell division.

The machinery that promotes asymmetric cell divisions has an evolutionarily conserved role in tumour suppression[2,72]. The *adenomatous polyposis coli* (*APC*) gene is required for the asymmetric division of *Drosophila* spermatogonial stem cells[29] and is an important tumour suppressor in the mammalian intestinal epithelium[73–75]. It is not known whether *APC* regulates asymmetric division by stem cells in the intestinal epithelium, but it is intriguing that, except for their unregulated proliferation, colorectal cancer cells have properties that are strikingly similar to those of intestinal epithelial stem cells[76]. The human homologue of *Lgl*, *HUGL-1*, is also frequently deleted in cancer[77,78], and deletion of the corresponding gene in mice leads to a loss of polarity and dysplasia in the central nervous system[79]. Loss of Numb may be involved in the hyperactivation of Notch pathway signalling observed in breast cancers[80,81]. Although these gene products could inhibit tumorigenesis through various mechanisms that are independent of their effects on cell polarity, the fact that these genes consistently function as tumour suppressors suggests that asymmetric division itself may protect against cancer.

Further evidence for the link between symmetric cell divisions and cancer is the observation that some gene products can both induce symmetric cell divisions and function as oncogenes in mammalian cells. One example is aPKC, the atypical protein kinase that normally localizes to the apical cortex of the neuroblast as part of the PAR–aPKC complex. Neural-specific expression of a constitutively active variant of aPKC causes a large increase in symmetrically dividing neuroblasts[42]. Consistent with this tumorigenic potential in *Drosophila*, *aPKC* has been also identified as an oncogene in human lung cancers[82,83]. We speculate that asymmetric division may suppress carcinogenesis, in addition to its role in maintaining a balance between stem cells and differentiated progeny.

Symmetric modes of division may not only promote the expansion of stem-cell numbers, but also be permissive for secondary events leading to aneuploidy. Consistent with this possibility, the machinery that controls asymmetric division also regulates the orientation of mitotic spindles[29,41,42]. A potential source of aneuploidy in symmetrically dividing fly neuroblasts is a defective centrosome — either duplicated or abnormal in shape — that presumably leads to errors in chromosome segregation[71]. The regulation of centrosome function by tumour suppressors is also important to avoid genomic instability in mammalian cells[84]. Indeed, centrosomes and mitotic spindles seem to be tightly regulated in asymmetrically dividing cells to ensure that daughter cells adopt different fates. It is tempting to speculate that tightly regulated

centrosomes can also protect chromosomes from errors in segregation. If so, symmetric divisions might not only increase stem-cell numbers, but also increase the probability of aneuploidy and other secondary mutations by loosening the controls on mitotic spindles.

Perspective

The prolonged symmetric divisions of mammalian stem cells during early embryonic development generate large pools of stem cells and tissues that are capable of repair. Perhaps the ability to switch back and forth between symmetric and asymmetric modes of division, depending on developmental and environmental cues, is a key adaptation that increases the capacity for repair and facilitates longer lifespan. A potential cost of the increased use of symmetric divisions by stem cells may be a higher incidence of cancer, particularly given circumstantial evidence that cancers frequently arise from the transformation of somatic stem cells[85,86]. Moreover, if tumour growth and progression are driven by cancer stem cells[85,86], then this process may remain biologically dependent on modes of division that permit the geometric expansion of stem cells.

The idea that symmetric divisions are required for neoplastic proliferation remains hypothetical, but raises the possibility that studies of the asymmetric division machinery could identify important new tumour-suppressor mechanisms. A key issue for the future is how stem cells are regulated to switch between asymmetric and symmetric divisions. A molecular understanding of this regulatory switch is not only relevant to basic stem-cell biology, but also has tremendous clinical importance for controlling stem cells therapeutically. ■

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