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Timing Cell-Fate Determination during Asymmetric Cell Divisions

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Abstract

From invertebrates to mammals, cell-cycle progression during an asymmetric cell division is accompanied by precisely timed redistribution of cell-fate determinants so that they segregate asymmetrically to enable the two daughter cells to choose different fates. Interestingly, studies on how cell fates are specified in such divisions reveal that the same fate determinants can be reiteratively used to specify a variety of cell types through multiple rounds of cell divisions or to exert seemingly contradictory effects on cell proliferation and differentiation. Here I summarize the molecular mechanisms governing asymmetric cell division and review recent findings pointing to a novel mechanism for coupling intracellular signaling and cell-cycle progression. This mechanism uses changes in the morphology, subcellular distribution and molecular composition of cellular organelles like the Golgi apparatus and centrosomes, which also accompany the progression of cell cycle, to activate but also temporally constrain the activity of fate determinants during asymmetric cell divisions.

Findings from decades of research on how cell fates are specified during development show that a given fate determinant is often capable of specifying multiple cell types and affecting seemingly contradictory aspects of cellular differentiation. A major challenge in developmental biology is to understand how the activities of such fate determinants are regulated, in particular how the cellular context – the presence and absence of other regulators – affects their ability to exert their influences. This review is not intended as a comprehensive overview of the known mechanisms of cell-fate determination but focuses on those involved in intrinsically asymmetric divisions by precursor cells in *Drosophila* and mice, particularly during neurogenesis. I summarize the mechanisms of asymmetric cell division and discuss recent findings that point to the potential use of cellular organelles like the Golgi and centrosomes to couple cell-cycle progression and cell-fate determination to allow for the reiterative use of fate determinants to specify multiple cell types or influence different aspects of cellular differentiation.

Patterns of cell division during neurogenesis

Intrinsically asymmetric cell division is a process that produces two daughter cells that are already different at birth. Such divisions are used extensively during *Drosophila* neurogenesis to produce the wide variety of neurons and glia necessary for building a functional nervous system. In the periphery nervous system (PNS), various sensory organs are produced through stereotypical divisions by single precursor cells [1]. An external sensory (ES) organ, for example, consists of four cells: a neuron, a sheath cell, a hair and a socket cell. The four cells

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are descendants of a single sensory organ precursor (SOP) cell through three rounds of asymmetric cell divisions (Figure 1a). The SOP cell first divides to produce a IIA and a IIB cell. The IIA cell then divides to generate a neuron and a sheath cell, whereas the IIB divides to generate a glial cell, which either moves away or dies, and a IIIB cell, which further divides to produce a neuron and a sheath cell. The precursor cells for other sensory organs, including the chordotonal organs, undergo similar patterns of divisions but generate different cell types.

In the *Drosophila* central nervous system (CNS), neurons and glia arise from precursors called neuroblasts. In *Drosophila* embryos, there are about 30 individually identifiable, segmentally reiterated neuroblasts, each divides repeatedly like a stem cell to generate a larger daughter cell that retains the neuroblast characteristics and bud off a smaller ganglion mother cell (GMC), which divides once, often asymmetrically, to generate two differentiated neurons and/or glia (Figure 1b). Each neuroblast has an invariant lineage tree, through which the origins of virtually all cell types in the embryonic CNS can be traced [2,3] (Figure 1B). Neurons and glia in the adult *Drosophila* brain are generated by neuroblasts in the larva. Larval neuroblasts generally divide in ways similar to that of their counterparts in the embryos, but their capacity to divide is considerably larger due to a need for producing much large numbers of neurons and glia. Moreover, unlike embryonic neuroblasts, which show similar division patterns and become smaller with each successive divisions, larval neuroblasts grow to their original size after each division and exhibit differences in division patterns. For example, the smaller daughter cell produced by neuroblasts of the dorsomedial lineage, instead of dividing only once like the GMC daughters in other lineages, also divide repeatedly [4].

While it remains unclear whether precursors in the developing mammalian nervous system generally undergo stereotypical divisions like their invertebrate counterparts, direct imaging experiments show that progenitor cells in the developing neocortex at least mostly divide asymmetrically. Radial glial cells (RGCs), which are the major population of cortical progenitor cells, undergo two types asymmetric divisions during cortical neurogenesis [5•, 6•]. In type-I divisions, a RGC divides to produce another RGC (self-renew) and a daughter cell that becomes a neuron (Figure 1c). In type-II divisions, a RGC divides in a way resembling that of the *Drosophila* neuroblasts by generating two daughter cells that both re-enter cell cycle, but one remains as a RGC whereas the other divides only once to generate two neurons (Figure 1c).

Mechanisms of asymmetric cell division

Studies using *C. elegans* and *Drosophila* show that generating two intrinsically different daughter cells requires at least three steps: a cell must first polarize itself so that one side of the cell is different from the other, followed by localizing various cell-fate determinants to only one side of the cell and aligning the mitotic spindle along the axis of cell polarity so that the localized fate determinants are segregated primarily to one of the two daughter cells. The molecules involved and their respective roles in establishing cell polarity and segregating cell-fate determinants have been extensively reviewed recently [7–9] and are briefly summarized below.

Cell polarity is established and maintained through the polarized distribution of two evolutionarily conserved protein complexes. One complex includes the Par proteins (Par3 and Par6) and atypical protein kinase C (aPKC), whereas the other comprises a protein cassette related to heterotrimeric G protein signaling that includes Gαi and Partner of inscuteable (Pins), which is a receptor-independent regulator of Gαi, as well as Inscuteable (Insc) and Discs-large (Dlg). The polarity of embryonic neuroblasts, which delaminate from the neural ectoderm, is aligned along the apical-basal axis. The Par proteins, which are already apically localized in the neural ectodermal cells, recruit Insc and the G protein cassette to the apical cortex during

neuroblast delamination. Subsequently, the Pax3/Par6/aPKC complex, through mechanisms that remain to be fully delineated but involve the tumor suppressor proteins Dlg and Lethal giant larvae (Lgl), helps to localize cell-fate determinants such as Numb (see more detailed discussion below), Prospero (Pros) and Brat to the opposite, basal cell cortex. The G protein related cassette, on the other hand, orients the mitotic spindle, at least in part through the Pins protein, which serves as a conformational switch linking Gαi and Mud. The latter is a *Drosophila* homologue of the microtubule and dynein binding protein NuMA, pointing to a model by which the apical complexes attract one of the spindle poles to orient the mitotic spindle along the apical-basal axis to ensure asymmetric segregation of the basally localized fate determinants [7–9].

In the *Drosophila* PNS, the polarity of SOP cells are aligned along the anterior-posterior body axis (planar polarity). SOP cells become polarized by responding to a planar polarity cue provided by the Wnt receptor Frizzled [10] and by localizing Gαi, Pins and Dlg to the anterior cell cortex [11,12]. The anterior Gαi/Pins/Dlg complex then directs the positioning of the Par3/Par6/aPKC complex to the posterior cortex, which in turns directs the accumulation of cell-fate determinants to the opposite (anterior) side of the cells. In other words, while the same players are involved in the critical steps of asymmetric cell division, different precursor cells use them differently. A good example is how the size difference between the two daughters is determined [11,13]. The two SOP daughters, IIA and IIB, are of similar size, whereas the GMC daughter of a neuroblast is considerably smaller than its sibling. Insc, an adaptor protein, helps neuroblasts to generate two differently sized daughter cells by binding to Pins through the GoLoco motif and recruiting Gαi/Pins complex to the Par3/Par6/aPKC complex [13]. Placing the two complexes on the same side of the neuroblasts results in an asymmetric mitotic spindle and, consequently, a cell cleavage plane that divides the cells unequally. Insc, however, is not expressed in SOP cells, and the Gαi/Pins/Dlg and Par3/Par6/aPKC complexes are localized to the opposite sides of the cell. This absence of Insc is important for SOP cells to generate a symmetric mitotic spindle and two similarly sized daughter cells, since Insc misexpression in SOP cells can lead to co-localization of the two complexes in one pole and asymmetry in daughter cell sizes [11].

Not surprisingly, the molecular components that regulate asymmetric cell division in *C. elegans* and *Drosophila*, including regulators of cell polarity like the Par proteins, aPKC, Insc, Pins and the components of G protein signaling as well as cell fate determinants like Numb, Pros and Brat, have highly conserved homologues in mammals. Like their invertebrate counterparts, the mammalian proteins show polarized distribution in mammalian neural progenitor cells, and perturbing their activities leads to defects in cell polarity, mitotic spindle orientation and daughter cell fates. The findings have been recently reviewed [7–9] and are not detailed here.

Reiterative use and diverse roles of cell-fate determinants

As summarized above, the key regulators of asymmetric cell division are evolutionarily conserved and used by precursors from *C. elegans* to mammals to establish cell polarity and orient mitotic spindle. Interestingly, although the precursor cells that divide asymmetrically, both in- and outside of the nervous system, often share no apparent class or lineage identities, many nevertheless use a common set of cell-fate determinants to distinguish their daughter cells. Numb, for example, is a cytosolic signaling protein that is widely expressed during embryogenesis and is segregated asymmetrically by a wide variety of neural and non-neural precursor cells to allow the two daughter cells to adopt distinct fates. In the CNS, neuroblasts are different from one another and bud off GMCs that produce morphologically and functionally distinct neurons and glia, and Numb can promote motor neuron over interneuron fates in some divisions but specify one interneuron fate over another in others [14,15]. Outside

of the nervous system, asymmetric Numb segregation is required for specifying different founder progenitor cells for various muscles as well as different cell types in the *Drosophila* Malpighian tubules (kidney) [16,17]. It is believed that Numb does not specify a particular fate but simply enables the two daughter cells to choose differently between two fate options. It has been further suggested that Numb does this by inhibiting Notch activity to cause a bias in Notch mediated cell-cell communication, either between the two daughter cells or between the daughter cells and their environment, through its asymmetric presence [18,19].

That Numb simply acts as a binary switch also raises an interesting question. In the SOP lineage, for example, Numb is used reiteratively in successive asymmetric divisions [1,20] (Figure 1a). It is symmetrically distributed during interphase but becomes localized to only one half of the cell membrane after the SOP cell enters mitosis and is segregated primarily into the IIB cell. This asymmetric Numb presence is essential; in the absence of Numb, both daughter adopt the IIA fate, whereas its symmetric inheritance produces two IIB cells. Interestingly, the IIA cell, which divides to produce a hair and a socket cell, also uses Numb to distinguish its two daughter cells. Even though the IIA fate requires Numb to be absent initially, newly synthesized Numb quickly accumulates in IIA cells, which then segregate the protein asymmetrically to promote the hair cell fate. In other words, Numb appears to lose its ability to specify cell fates shortly after an asymmetric division but regains the ability to do so when the cells divide again.

The mammalian Numb homologues are encoded by two genes, *m-numb (Numb)* and *numblike (Numbl)* [21–24]. The two genes are functionally redundant during mouse neurogenesis and are expressed in both neural progenitor cells and neurons [24,25]. They are essential for neurogenesis but play two seemingly contradictory roles in this process. When neural progenitor cells divide asymmetrically to self-renew and produce a neuron, Numb proteins segregate asymmetrically to promote progenitor over neuronal fates [25,26]. After the division, however, they are required for the differentiation of newborn neurons [25,27]. In other words, the ability of mammalian Numb proteins to specify cell fates may also be limited to during and/or shortly after mitosis.

Golgi Fragmentation and Numb signaling

That cells whose fates depend on an initial Numb absence subsequently use Numb to specify the fates of their daughter cells or promote their own differentiation raises an interesting possibility that Numb activity in cell-fate specification is tightly regulated and coupled to cell-cycle progression. Our recent study points to a novel mechanism that uses the process of Golgi fragmentation and reconstitution during cell cycle to differentially regulate Numb signaling by changing the subcellular distribution of an essential partner of Numb, ACBD3, thereby allowing Numb signaling to be activated only at times when the two daughter cells are being generated and be deactivated shortly after they are born [28••].

Cell-cycle progression in mammalian cells is accompanied by dramatic changes in the morphology of the Golgi apparatus, an essential organelle that plays a variety of roles, including post-translational modification and trafficking of proteins. Mammalian Golgi membranes are organized into interconnected stacks of flattened cisternae during interphase and confined to the region surrounding the centrioles. When cells enter mitosis, however, they fragment the pericentriolar Golgi stacks and disperse the Golgi fragments throughout the cytosol to ensure that both daughter cells inherit this essential organelle, although there is debate as to whether the Golgi simply disappears and is regenerated after the division from the endoplasmic reticulum (ER) [29–31].

ACBD3 binds to Numb through a functionally essential Numb domain and can act synergistically with Numb to specify cell fates. Like mammalian Numb proteins, ACBD3 is widely expressed and present in both neural progenitor cells and neurons. However, unlike

Numb and Numbl, which are cytosolic proteins, ACBD3 associates with the Golgi in postmitotic neurons and interphase progenitor cells (Figure 2a). After the Golgi fragments during mitosis, however, ACBD3 is released into the cytosol. In other words, the two partners, Numb and ACBD3, may only be able to interact with each other during mitosis, when Numb activity is needed to distinguish the daughter cells, and the ability of Numb to specify cell fates is quickly lost after the division as ACBD3 goes back to the Golgi, thereby allowing Numb to promote differentiation of newborn neurons by tapping into a different pathway or to wait for reactivation until the next division (Figure 2b). This model is supported by experiments using a myristoylated form of ACBD3, which remains in the cytosol throughout the cell cycle. As expected, this cytosolic form of ACBD3 can specify cell fates in the presence of Numb, and, more importantly, its misexpression in neural progenitor cells during mouse neurogenesis inhibits neuron production, likely by forcing both daughter cells to choose progenitor over neuronal fates [28].

It is worth noting that ACBD3 release into the cytosol likely is not simply a byproduct of Golgi fragmentation but rather a precisely regulated process. Golgi fragmentation is tightly coupled with cell-cycle progression. It occurs before cells enter prophase and is actually essential for entrance into mitosis [32]. ACBD3 associates with the cytoplasmic face of Golgi membranes and remains associated with fragmented Golgi fragments (blobs) until late metaphase, when it becomes mostly cytosolic [28]. Since the Golgi also further fragments and releases some of its contents between pro-metaphase and early anaphase [30], it will be interesting to determine whether and how the regulators of Golgi fragmentation and reconstitution affect ACBD3 distribution.

Cell-cycle regulators and centrosomes in asymmetric cell division

It is unclear whether and how this Golgi-based mechanism is conserved evolutionarily. In *Drosophila* embryos, the Golgi exists as widely dispersed units in the cytoplasm and does not further fragment during cell cycle [33]. ACBD3, however, has a highly conserved *Drosophila* homologue, and mammalian Numb and ACBD3 proteins can function synergistically to specify Numb-dependent fates in *Drosophila.* Therefore, at least some aspects of this novel mechanism are likely to be evolutionarily conserved. Moreover, since the steps of asymmetric cell division, including precisely timed redistribution of cell-fate determinants, are intimately associated with the phases of cell cycle, it is likely that the Golgi apparatus is not the only organelle used by cells to activate and also temporally constrain the activities of fate determinants. There is evidence that this may indeed be the case.

In *Drosophila,* Numb, Pros and Brat are symmetrically distributed in interphase cells but becomes asymmetrically localized by metaphase. Their asymmetric localization is mediated by two adaptor proteins, Partner of Numb (Pon), which binds to Numb, and Miranda, which bind to Pros and Brat [34–38]. Interestingly, whereas Miranda is essential for asymmetrically localizing Pros and Brat, Pon loss only delays Numb asymmetric localization, which nevertheless occurs by the time cells enter into anaphase and telophase [36]. The latter phenomenon, termed “telophase rescue”, which is observed in many mutants affecting asymmetric cell division, results from the presence of a pathway involving Kinesin heavy chain 73 (Khc-73), a plus-end-directed microtubule motor protein, and Dlg, the membrane-associated guanylate kinase (MAGUK) [39]. The Khc-73/Dlg pathway and the previously described Par3/Par6/aPKC/Insc pathway can both generate cell polarity by asymmetrically localizing Gαi/Pins but act independently and during different phases of the cell cycle. The Par3/Par6/aPKC/Insc pathway is initiated at late prophase by an unknown extrinsic cue, whereas the Khc-73/Dlg pathway is initiated later during prometaphase/metaphase by astral microtubules and is required for Gαi/Pins localization over the spindle pole (but only when Par and Insc proteins are absent).

Cell-cycle progression is driven by changes in the activity of cell-cycle regulators, and several such regulators, including Cdc2, Aurora-A and Polo, have been shown to be critical for asymmetric Numb localization [40–44]. Cdc2 is a Cyclin-dependent kinase and essential for entry into mitosis, whereas Aurora A and Polo are involved in many events during mitosis, including centrosome maturation, spindle formation and cytokinesis. Cdc2 is not required for initiating the formation of the apical complexes but is necessary for its maintenance and, consequently, the asymmetric localization of cell fate determinants [40]. Attenuating the function of Aurora-A [41••,44] or Polo [43••], while leaving many components of the polarity complexes unaffected, causes aPKC and Numb to distribute symmetrically in dividing neuroblasts and SOP cells. Most importantly, although Numb segregates symmetrically in *cdc2*, *aurora-A* and *polo* mutants, the phenotypes exhibited by these mutants are actually consistent with a loss of Numb function. Since Numb asymmetric localization is not essential for the ability to specify cell fates [24,45], these findings indicate that the cell-cycle regulators may also be required, directly or indirectly, for activating Numb signaling, thereby constraining Numb activity to during and shortly after mitosis. A recent study also points to another way of bringing two signaling partners together in a cell-cycle dependent manner. Bora, a nuclear protein, is required for the activation Aurora-A, which is present in the cytoplasm and also associates with the centrosomes. Interestingly, upon entry into mitosis, Bora becomes excluded from the nucleus in a Cdc2-dependent manner, pointing to a model that entrance into mitosis initiates the release of Bora into the cytoplasm to activate Aurora-A [42•]. Once Aurora-A is activated, if further triggers a phosphoryaltion cascade that at least is responsible for asymmetric Numb localization [41••]. In SOP cells, Lgl, Par-6 and aPKC form a complex at one pole. Aurora-A first phosphorylates Par-6, a regulatory subunit of aPKC, to activate aPKC, which in turn phosphorylates Lgl. A consequence of Lgl phosphorylation is the exchange of Lgl for Bazooka (the *Drosophila* Par-3 homologue) in the complex, and this changes the substrate specificity of aPKC, which then phosphorylates Numb and releases it from one side of cortex, thereby causing Numb to concentrate on the other side of the cell cortex.

In addition to the changing activities of cell-cycle regulators, progression through cell cycle is also accompanied by changes in the centrosome. Centrosomes are duplicated during S phase, and migration of the two centrosomes to the opposite poles of the cells during prophase and the subsequent formation of the mitotic spindle are essential for asymmetric cell division to occur by ensuring that the localized cell-fate determinants are segregated asymmetrically. Several recent studies, however, indicate that the importance of centrosomes during asymmetric cell division is not simply due to its roles in organizing the poles of the mitotic spindle; centrosomes may play a more direct role in regulating asymmetric cell division. *Drosophila* larval neuroblasts with extra centrosomes initially form multiple spindles. This, however, triggers the spindle assembly checkpoint, which in turn delays the progression of mitosis. Subsequently, the delay in mitosis enables the cells to either cluster the centrosomes at the two poles or inactivate those that are not clustered, and the spindles eventually become bipolar, allowing the cells to generate two daughters that maintain a stable diploid genome. Interestingly, despite the eventual presence of a bipolar mitotic spindle, some neuroblasts exhibit defects in polarized distribution of proteins involved in asymmetric cell division and divide symmetrically instead of asymmetrically, leading to tumor-like growth of neuroblasts as both daughter cells choose self-renewal over differentiation [46••]. Most intriguingly, the male germline stem cells (GSCs) in *Drosophila*, which divides asymmetrically to self-renew and produce a daughter cell that differentiates, segregate the two centrosomes non-randomly. Differential labeling of mother and daughter centrosomes reveal that the mother centrosome, which contains the oldest centriole, is consistently inherited by the daughter cell that will remain as a GSC [47••]. While the importance of this non-random segregation of the two centrosomes remains to be determined, it is conceivable that the two centrosomes may harbor different cell-fate determinants or their regulators that help to determine daughter cell fates [48].

Conclusions

The studies described above show that the mechanisms of asymmetric cell division – establishing and maintaining cell polarity, controlling mitotic spindle orientation and localizing cell-fate determinants – are highly conserved evolutionarily and such divisions are essential for development and for stem cells to balance self-renewal and differentiation from invertebrates to mammals. These studies also pose an interesting challenge – namely, to elucidate the molecular mechanisms that allow the same cell-fate determinants to be reiteratively used and play diverse roles. A hallmark of asymmetric cell division is that its regulation is precisely coordinated with the progression of cell cycle, which is also accompanied by a variety of other cellular changes, from the activities of cell-cycle regulators themselves to the morphology, distribution and molecular contents of organelles and other subcellular components. Numb signaling likely is not the only pathway taking advantage of Golgi fragmentation and reconstitution to couple its activation with cell-cycle progression. Therefore, further examination of how the activity of cell fate determinants are activated and constrained during asymmetric cell divisions may reveal novel mechanisms that integrate cellular signaling in a context dependent manner to regulate development and the behavior of stem cells.

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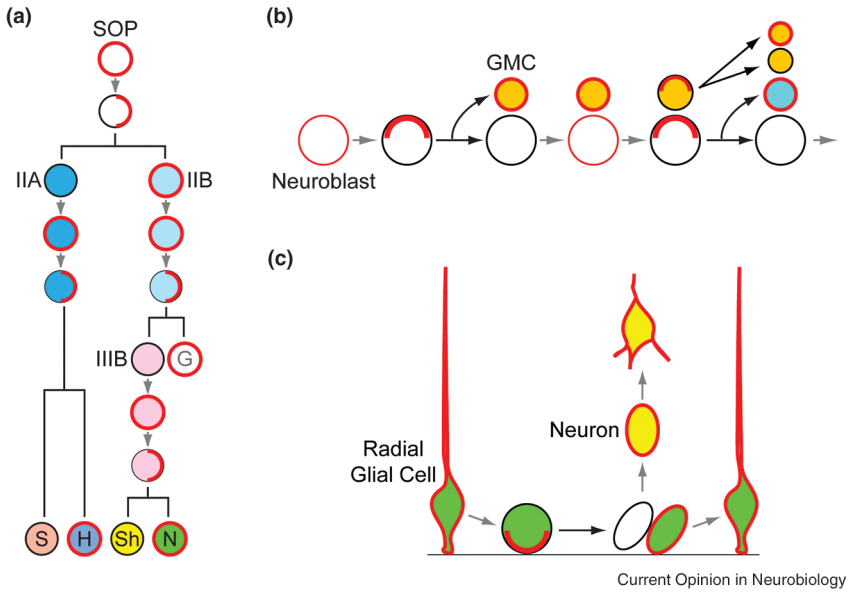

Figure 1.
Reiterative use and diverse roles of the cell-fate determinant Numb during asymmetric cell divisions. (a) *Drosophila* SOP cells. (b) *Drosophila* neuroblasts. (c) Mammalian radial glial cells. G, glial cell; H, hair cell; N, neuron; S, socket cell; Sh, sheath cell.

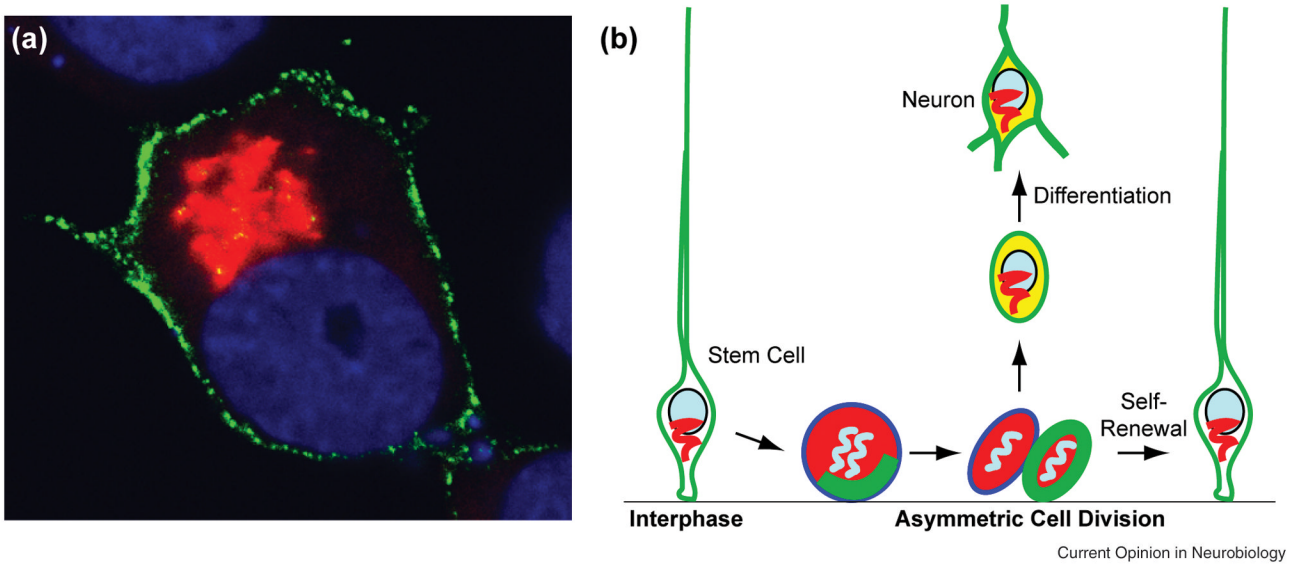

Figure 2.

A Model for differentially regulating Numb signaling during mammalian neurogenesis through Golgi fragmentation and reconstitution. (a) The subcellular distribution of the exogenous, GFP-tagged mouse Numb protein (in green) and the endogenous ACBD3 (in red) in interphase NIE115 cells, a mouse neuroblastoma cell line. (b) Numb proteins promote self-renewal when neural stem (progenitor) cells divide asymmetrically to self-renew and produce a neuron, but this occurs only when ACBD3 (in red) is present in the cytosol after Golgi fragmentation during mitosis. Newly synthesized Numb proteins subsequently accumulate in newborn neurons but, with ACBD3 localized to the Golgi, tap into a different pathway to promote neuronal differentiation. Stem cells in many tissues may use this mechanism to balance self-renewal and differentiation.