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REVIEW

SPECIAL ISSUE: CELL AND TISSUE POLARITY

The contribution of asymmetric cell division to phenotypic heterogeneity in cancer

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ABSTRACT

Cells have evolved intricate mechanisms for dividing their contents in the most symmetric way during mitosis. However, a small proportion of cell divisions results in asymmetric segregation of cellular components, which leads to differences in the characteristics of daughter cells. Although the classical function of asymmetric cell division (ACD) in the regulation of pluripotency is the generation of one differentiated daughter cell and one self-renewing stem cell, recent evidence suggests that ACD plays a role in other physiological processes. In cancer, tumor heterogeneity can result from the asymmetric segregation of genetic material and other cellular components, resulting in cell-to-cell differences in fitness and response to therapy. Defining the contribution of ACD in generating differences in key features relevant to cancer biology is crucial to advancing our understanding of the causes of tumor heterogeneity and developing strategies to mitigate or counteract it. In this Review, we delve into the occurrence of asymmetric mitosis in cancer cells and consider how ACD contributes to the variability of several phenotypes. By synthesizing the current literature, we explore the molecular mechanisms underlying ACD, the implications of phenotypic heterogeneity in cancer, and the complex interplay between these two phenomena.

KEY WORDS: Asymmetric cell division, Sister cells, Cancer heterogeneity, Cell division, Fitness

Introduction

Mitosis has evolved to be symmetric in most cases, as indicated by the complex machinery that equally segregates chromosomes to daughter cells. All other cellular components are divided by the mitotic furrow, which produces nearly symmetric partitioning as long as the mother cell has a homogeneous distribution of these components. This results in symmetric cell division (SCD) (Duan and Sun, 2019; Leonard and Grimwade, 2009; Pajpach et al., 2021). However, cells can actively target components to a particular subcellular region during division, and stochastic fluctuations in the distribution or localization of the mitotic cleavage furrow can create asymmetries, producing an asymmetric cell division (ACD) (see Box 1). ACD influences cell fate outcomes and is essential for development and tissue homeostasis. During the first division of the zygote, the animal and vegetal poles contain very different proteins and RNAs, leading to highly asymmetric daughter cells and subsequent lineages (Beddington and Robertson, 1999; Chen et al., 2018; Cooke, 2004). ACD is also associated with division of self-renewing stem cells. Mother stem cells can show plasticity in their mode of division and are able to either divide symmetrically, generating two stem cells or two differentiated cells, or asymmetrically, generating one stem cell and one differentiated cell (Wu et al., 2007). Balancing these division modes is crucial to ensuring tissue homeostasis and regeneration (Simons and Clevers, 2011), making ACD a physiological mechanism of homeostasis. The balance of ACD and SCD shapes tissues such as the cerebral cortex, whose size is determined by the timing of a shift from SCD, which generates only neural precursor cells, to ACD that produces one precursor cell and one differentiated neuron (Rakic, 2009).

Phenotypes and markers of normal stem cells have also been observed in subpopulations of cancer cells; such cells are often termed cancer stem cells (CSCs) (Magee et al., 2012). CSCs have the capacity, via ACD, to maintain a proportion of self-renewing tumor cells with stem cell characteristics, as well as a proportion of cells without these attributes. These self-renewing subpopulations are associated with intratumoral heterogeneity (ITH) (see Box 2) and the emergence of more aggressive cancer subtypes (Liu et al., 2013; Pine et al., 2010). For example, the disruption of the balance between ACD and SCD in colon cancer gives rise to more aggressive tumors, which contain higher pools of CSCs and are associated with resistance to therapy and poor prognosis in patients (Bu et al., 2013; Hwang et al., 2014). ITH is intertwined with the concept of cell fitness, one of the most important cellular phenotypes involved in cancer. Cell fitness is defined as the number of descendants produced by a given cell or population over a given time, which is thus the sum of the positive impact of cell proliferation and the negative impact of cell death. Cell fitness can be impacted by the asymmetric inheritance of components or phenotypes to one of the daughter cells in ACD. However, it is unclear whether ACD in cancer occurs exclusively in CSCs, and the molecular mechanisms underlying the occurrence of ACD in cancer and how they ultimately influence cell fitness and phenotypic ITH are not fully understood.

In this Review, we will discuss cell components and phenotypes that can be asymmetrically distributed between sister cells in cancer, focusing on the impact these asymmetries have on cell fate, fitness, generation of ITH and, ultimately, on cancer pathology.

Asymmetric distribution of cell components in cancer

Several cellular components or features can be asymmetrically divided in both normal and cancer cells. As multiple components and phenotypes can show asymmetric distribution, defining exactly what qualifies as an ACD requires careful selection of experimental criteria (see Box 1). We will next discuss specific components that have been shown to exhibit asymmetric inheritance in cancer cells, such as chromosomes, centrosomes, epigenetic markers and organelles (Fig. 1A). Table 1 lists studies that have shown

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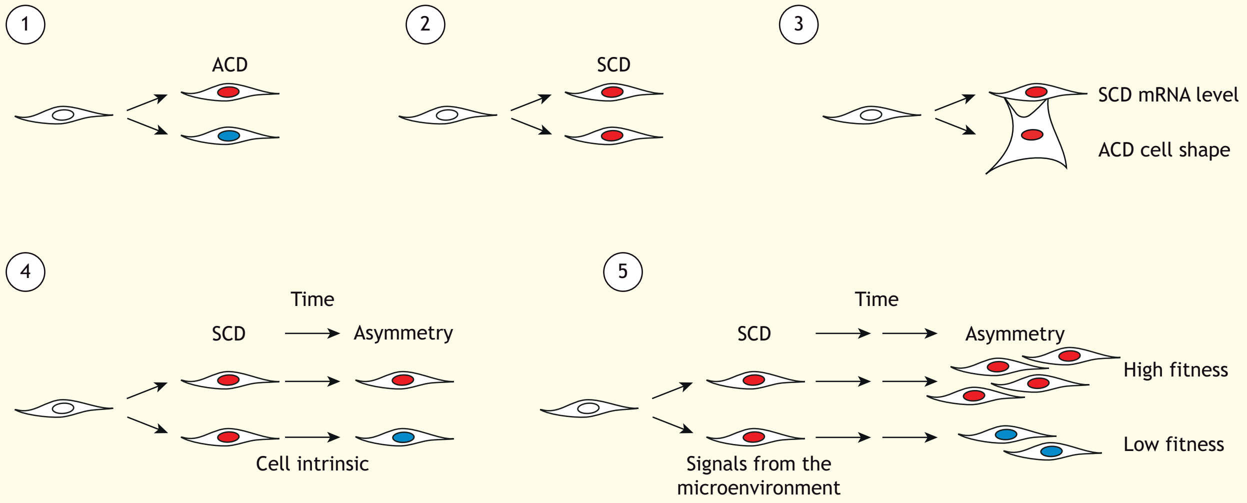
Box 1. How to define an ACD

An ACD is a cell division that produces daughter cells in which one cell is different from the other cell in a measurable feature such as mRNA expression of a certain gene (represented in the accompanying figure as the nucleus color) or cell morphology (represented as a cell shape). Sister cells can be asymmetric in a single feature or in several features. Defining which component or phenotype the symmetry of the division refers to is central to determining an ACD. If multiple features are analyzed, one might be divided symmetrically and the other asymmetrically, as shown in the figure. In theory, most divisions could be considered asymmetric if all features were measured with great precision. This makes the choice of the feature being analyzed fundamental.

Symmetry breaking (bottom left of figure) of a given feature can occur right after mitosis, over the course of the next cell cycle or after later rounds of division, as shown in the figure. Assessing symmetry right after division is the most widely used method to define ACD and SCD. However, an apparent SCD can eventually lead to asymmetries between two sister cells over the time course of their next cell cycle (Wu et al., 2007) or among their descendants (Yang et al., 2022). Such asymmetries can result from cell intrinsic differences or from external signals from the microenvironment. Great care must be given to identifying true positive ACDs in fixed cells, as such analyses lack prior and future time points for comparison (Loeffler et al., 2019).

Cell fitness (bottom right of figure) is most commonly defined as the number of descendants of a single cell after a given time. If two branches derived from a single cancer cell generate a different number of descendants, then the division can be considered asymmetric in regards to fitness. Therefore, the two lineage branches of a cell division should be included in the criteria when determining the symmetry of a division, especially in cancer biology in which cell fitness is a key feature.



asymmetric segregation of various cellular components and the co-occurrence of stem cell markers in cancer cells that performed ACD.

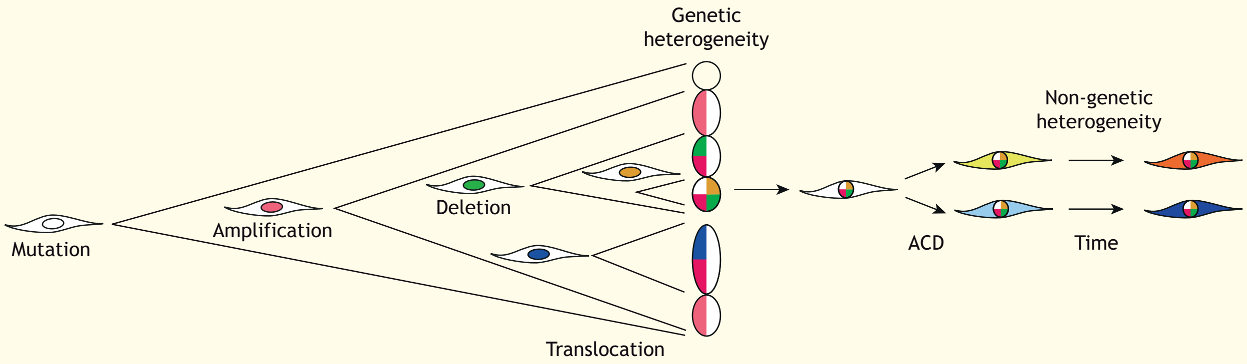
Asymmetric segregation of chromosomes and DNA

Malfunction of the complex machinery that has evolved to guarantee complete symmetry of the division of chromosomes can produce aneuploidy and strongly contributes to tumorigenesis (Jordan and Wilson, 2004; Sansregret and Swanton, 2017). Aneuploidy, which can result in increased expression of oncogenes or reduced expression of tumor suppressor genes, is one of the hallmarks of cancer and is associated with tumor evolution and interpatient variability (Black and McGranahan, 2021; Hanahan and Weinberg, 2000, 2011). The spindle assembly checkpoint (SAC) is responsible for equal segregation of chromosomes and only allows the progression of mitosis if all chromosomal centromeres are linked to microtubules, thus exerting a combined pull (Lara-Gonzalez et al., 2012; Musacchio and Salmon, 2007; Silva et al., 2011; Tauchman et al., 2015; Walker, 2022). Increasing evidence suggests that chromosome segregation errors are non-random, with certain chromosomes presenting greater propensity to contribute to aneuploid karyotypes than others (Fontebasso et al., 2015; Klaasen and Kops, 2022; Kumar et al., 2018). The main factors associated with this phenomenon are chromosome size and chromosome nuclear location (Klaasen et al., 2022), and centromere features such as size of centromeres (Drpic et al., 2018), levels of centromeric cohesin molecules and presence of mutations or deletions in cohesin genes (Solomon et al., 2011). Aneuploid cancer cells are less sensitive than euploid cells to SAC inhibition, resulting in the accumulation of mitotic defects and unstable and less-fit karyotypes (Cohen-Sharir et al., 2021). Active generation of aneuploidy also occurs during neurogenesis, in which aneuploidy of chromosome 21 appears in ∼4% of cells in the human brain, compared to a rate of 0.6% in lymphocytes (Rehen et al., 2005). This suggests the existence of a mechanism for controlled generation of aneuploidy. Whether asymmetric segregation of chromosomes in cancer is simply a malfunction of the mitotic machinery or a reactivation of this mechanism is still an open question.

Asymmetric DNA template segregation occurs when chromosomes containing the ‘old’ template strand inherited from previous divisions are preferentially segregated to one daughter cell, while the other receives only ‘new’ synthesized template. The non-random segregation of original DNA templates is thought to protect the integrity of the genome by retaining the original copy of the DNA within the self-renewing cells, thus preventing the accumulation of mutations during replication (Cairns, 1975). Another explanation for this is the presence of different epigenetic markers among the copies of chromosomes which direct divergent cell fates in sister cells (Lansdorp, 2007). Cancer cells might use this mechanism to maintain a pool of self-renewing cells. In triple-negative breast cancer, the asymmetric segregation of template DNA strands is most evident in basal-like cancers, which have large

Box 2. Intratumor heterogeneity

ITH is defined as all the heterogeneity among the cells that compose a tumor. This heterogeneity can be genetic, epigenetic, transcriptomic, proteomic or in any other component that changes the phenotype of the cancer cell (Lenz et al., 2022). Because heterogeneity can be vast, focus must be given to the types of heterogeneity that matter most in cancer. These are typically heterogeneities that influence cell fitness by, for example, increasing the probability of division, of tolerance to therapy or the immune system, or decreasing the probability of cell death. The relative contribution of genetic and non-genetic sources of heterogeneity is highly variable and ACD can generate heterogeneity through both genetic and non-genetic alterations. The figure below shows a stylized lineage tree of a population of tumor cells deriving from a single cancer cell. Genomic alterations (represented in the accompanying figure as different nucleus colors), such as mutations, amplifications, translocations and deletions, generate much of the genetic heterogeneity in cancer. ACD contributes to phenotypic heterogeneity (represented as different cell colors) even in cells with the same genetic background.



self-renewing cell subpopulations that display increased migration and invasion potential (Al-Hajj et al., 2003; Liu et al., 2013). In lung cancer, cells can asymmetrically co-segregate their 'old' DNA template along with the stem cell marker CD133 (also known as prominin-1; PROM1) to one of the daughter cells during mitosis. When isolated and allowed to regrow, these cells are capable of generating a cell population with a similar phenotypic heterogeneity of the original population (Pine et al., 2010), confirming capacity for self-renewal and the generation of tumor heterogeneity.

Extrachromosomal DNA (ecDNA) can occur in multiple copies. Because ecDNA lacks centromeres, it is not segregated by the mitotic spindle and thus is usually randomly segregated. ecDNA containing cancer driver genes can be unequally distributed between daughter cells (Lange et al., 2022). This produces extensive intratumoral ecDNA copy number heterogeneity, resulting in fast adaptation to treatment and metabolic stresses. The continuous stochastic segregation of ecDNA contributes to adaptability of the cancer genome, making the asymmetric segregation of ecDNA an important player in aggressive phenotypes of certain cancers.

Centrosome amplification, an abnormal increase in centrosome number or size, is a common feature of cancer cells. Given that centrosome amplification affects the bipolarity of the mitotic spindle, it drives ACD in chromosome number and in the number of centrosomes inherited by each daughter cell (Fukasawa, 2005; Gisselsson, 2005). Even in the absence of additional genetic defects, centrosome amplification causes aneuploidy and drives the development of spontaneous tumors in multiple tissues in mice (Levine et al., 2017), highlighting the important role ACD of genetic material plays in tumorigenesis. In addition, it has recently been shown that centrosome amplification controls intracellular organelle organization and promotes the displacement of mitochondria, centrosomes and vimentin (Monteiro et al., 2023), which might promote ACD of these cellular components. In pancreatic cancer cells, the presence of extra centrosomes induces small extracellular vesicle secretion as a result of lysosomal dysfunction, which leads to promotion of malignancy through increased invasion of pancreatic cancer cells in heterotypic 3D cultures (Adams et al., 2021).

Asymmetric division of cell fate determinants and stem-like markers

The mechanisms that promote genetic duplication and portioning during mitosis are well understood, but the same is not true for how epigenetic and non-genetic information is copied and separated between sister cells. One key non-genetic driver of cell fate determination is the classical epigenetic signature of the cell. This includes the chromatin state, which is defined by DNA modifications together with histone composition, post-translational modifications and associated proteins. In *Drosophila* male germline stem cells, pre-existing histones are preferentially maintained in the stem cell, whereas newly synthetized histones are inherited by the differentiating daughter, potentially allowing the new histones to be modified to promote a new cell fate (Wooten et al., 2019). In mammalian cells, the role of this mechanism remains elusive but the emergence of new technologies for single-cell analysis has allowed the discovery of asymmetric distribution of histones during mitosis in mouse embryonic stem cells (Ma et al., 2020a,b). If this asymmetric inheritance of histones occurs in cancer cells or CSCs, and whether this has any effect on tumorigenesis are still open questions.

Another epigenetic component that plays a role both in ACD and in cell fate decision are microRNAs (miRNAs). miRNAs alter gene expression by binding to target mRNAs, inhibiting their translation or flagging them for degradation (Wooten et al., 2019). Thus, miRNAs have an important function in the regulation of cell fate decisions during development, tissue homeostasis and oncogenesis (Hill and Tran, 2021). For example, miRNAs have been implicated in regulating the balance between ACD and SCD in colon cancer (Bu et al., 2013, 2016; Hwang et al., 2014). The tumor suppressor miR-34a is asymmetrically divided in colon CSCs, generating one differentiating daughter cell with high miR-34a levels and one self-renewing daughter with low miR-34a levels (Bu et al., 2013). miR-34a expression is regulated by a long non-coding RNA, Lnc34a, that directly targets the miR-34a promoter for epigenetic silencing by

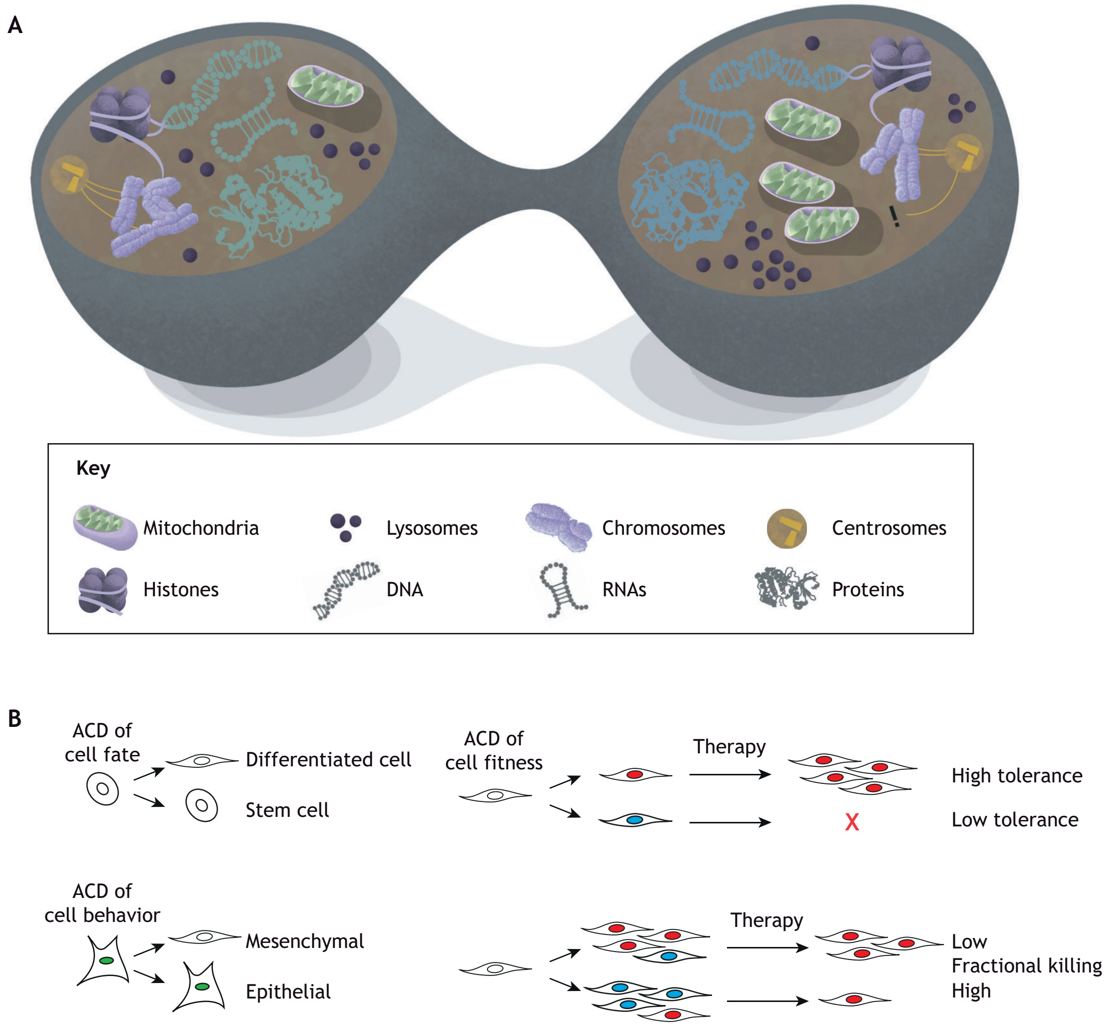


Fig. 1. Asymmetric division of cell components and phenotypes. (A) Components such as chromosomes, DNA templates, centrosomes, histones, RNAs, proteins and organelles can undergo asymmetric distribution during ACD in cancer cells. Asymmetric division of 'healthy' versus damaged structures, such as mitochondria, has also been suggested to influence cancer cell fate and fitness. (B) Examples of phenotypes that can be asymmetrically divided in cancer cells. CSCs can undergo ACD and give rise to one self-renewing cell and one differentiated cell. ACD is also relevant in pro-invasion phenotypes such as epithelial-to-mesenchymal transition (EMT), as one daughter cell might inherit factors that promote EMT. Such asymmetric inheritance of phenotypes leads to differences in cell fitness over time or in response to therapy, creating distinct populations of cancer cells which can vary in population number or treatment sensitivity and the degree of fractional killing.

recruiting the DNA methyltransferase Dnmt3a and histone deacetylase 1 (HDAC1) (Wang et al., 2016). High levels of miR-34a suppress translation of NUMB, an important developmental regulator of cell fate in ACD, directing one of the daughter cells toward differentiation (Bu et al., 2016). Loss and gain of miR-34a function alters the balance between self-renewal versus differentiation fates, leading to more SCDs with subsequent generation of two stem cells or two differentiated cells (Bu et al., 2013). Similarly, miR-146a, a miRNA that is expressed in the presence of the epithelial-to-mesenchymal transition (EMT) inducer Snail (SNAI1), is responsible for the ACD-to-SCD switch in colon CSCs through suppression of NUMB, a phenotype that is associated with resistance to therapy and poor prognosis in patients (Hwang et al., 2014).

Several proteins associated with stem-cell-like phenotypes, such as CD133, CD44, Oct4 (also known as POU5F1), Sox and Nanog, are asymmetrically expressed during ACD in certain cancer subpopulations, and likely contribute to defining cell fate and generating ITH (Magee et al., 2012). Breast cancers are composed of highly phenotypically heterogeneous cell populations, including a distinct subpopulation expressing a combination of stem cell markers (CD44^{+}/CD24$^{-/\text{low}}$). These cells show a high capacity to form tumors, whereas subpopulations with other combinations of markers have less tumor-initiating capability (Al-Hajj et al., 2003). Importantly, isolated CD44^{+}/CD24$^{-/\text{low}}$ homogeneous subpopulations can generate new tumors that contain additional CD44^{+}/CD24$^{-/\text{low}}$ tumorigenic cells, as well as phenotypically diverse mixed populations of non-tumorigenic cells like those present in the initial tumor (Al-Hajj et al., 2003), highlighting the ability of these cells to asymmetrically distribute CSC markers and form phenotypically heterogeneous populations. In a similar way, a subpopulation of thyroid cancers cells that asymmetrically divides the progenitor marker stage-specific embryonic antigen 1 (SSEA-1; also known as B3GALT5) was also shown to express additional stem cell markers, including Oct4, Sox2 and Nanog, and possessed tumor-initiating properties and resistance to chemotherapy (Ma et al., 2014).

Table 1. ACD of different cell components in cancer cells

Component	Stem cell marker	Cell line or source	Main results	Reference
Double minute chromosomes (DMs)	NA	COLO320 cells with DMs containing an amplified Myc gene infected with the H2B–GFP retrovirus	Uneven distribution of DMs to daughter cells after cytokinesis.	Kanda et al., 1998
DNA template and CD133	CD133	Human lung cancer cells (A549 and H441)	Lung cancer cells can asymmetrically divide their template DNA; frequency of ACD is increased by cell–cell contact.	Pine et al., 2010
DNA template and CD44	CD44	Breast cancer cell lines	Positive correlation between asymmetric segregation of template DNA and the breast cancer basal-like and claudin-low subtypes.	Liu et al., 2013
Mitotic spindle	NA	HEK293 and H929 cells	The combination of TP53 knockout and NEK2 overexpression induces asymmetric spindle division *in vitro* and *in vivo.*	Feng et al., 2022
Centrosomes	CD133	Neuroblastoma cells (SH-SY5Y)	Cells with a single copy of MYCN showed significantly higher percentages of ACD than those with MYCN amplification.	Izumi and Kaneko, 2012
Numbers of centrioles	NA	Primary cultures of myeloid leukemia and glioblastoma	Asymmetric centriole rosettes generate mitotic errors that cause chromosome missegregation in cancer.	Cosenza et al., 2017
Inclusion bodies	NA	PC12 with an inducible Huntingtin (Htt)	Daughter cell that inherits the inclusion body has decreased proliferation, increased differentiation and stress resistance compared to its sister cell.	Bufalino and van der Kooy, 2014
miR-34a	NA	Colon CSCs	miR-34a and NUMB are both present in the same daughter cells in 82% of divided pairs and act as stem fate determinants.	Bu et al., 2016
miR-34a	CD133	Human colon cancer cells (Colo205, SW480, HT29, SW620, LS174T, DLD1, Caco-2)	Lnc34a promotes CCSC self-renewal, and Lnc34a asymmetry leads to cell fate asymmetry in CCSC division.	Wang et al., 2016
CD133 marker in a fraction of GSCs	CD133	Glioma stem cells from individuals with newly diagnosed (T4302) or recurrent (T4121) glioma	Under growth factor withdrawal conditions, the proportion of asymmetric CD133 divisions increased.	Lathia et al., 2011
MYCN and Trim32	CD133	Human neuroblastoma cells	Trim32 facilitates degradation of MYCN on spindle poles and induces asymmetric cell division in human neuroblastoma cells.	Izumi and Kaneko, 2012
SSEA-1 (a marker for CSCs in brain tumors)	OCT4, SOX2, NANOG	Thyroid cancer cell lines (T238)	Asymmetric inheritance of SSEA-1 is correlated with CSC markers and promotes resistance after chemotherapy.	Ma et al., 2014
GFAP (intermediate filaments responsible for cytoplasm organization)	CD15, CD133, CD44, SOX2, OLIG2	GBM primary culture and neural stem cell cultures	GFAP can segregate asymmetrically (at a frequency less than 10% of division) in multipotent GBM and non-tumoral neural cell division.	Guichet et al., 2016
CD53, CD62L (L-selectin), CD63 (Lamp-3), CD71 (transferrin receptor)	CD133, CD44	HPCs	CD53, CD62L, CD63 and CD71 segregate differentially in ∼20% of primitive human hematopoietic cells in stroma-free cultures.	Beckmann et al., 2007
NUMB, EGFR, NESTIN, GFAP	NESTIN, SOX2, MUSASHI1, vimentin, CD15 and CD133	Brain tumor-initiating cells (BTIC lines)	Asymmetric division of EGFR, NUMB, NESTIN and GFAP is observed in BTIC lines.	Cusulin et al., 2015
EGFR	CD44 and CD95	Squamous cell carcinoma (A431), primary basal cell carcinoma	Normal and cancerous keratinocyte fate has been linked to the asymmetric distribution of EGFR during mitosis.	Le Roy et al., 2010
PKCζ protein	NA	Jurkat cells	PKC inherited asymmetrically in 2.5% of all telophasic events.	Filby et al., 2011
Ras (p21), ERBB-2 (p185), Fos (p55), Myc (p62)	NA	T24, HeLa S3 MCF-7, SW-620	The uneven distribution of oncogene-encoded in tumor cells causes phenotypic heterogeneity the lack of synchronization in the cell cycle.	Czerniak et al., 1992
AKT (PKB) kinase activity	NA	Breast cancer cells	Suppression of AKT (PKB) kinase signaling during telophase promotes the birth of a slowly cycling cancer cell (G0-like cancer cells).	Dey-Guha et al., 2011

NA, not assessed; OSCC, oral squamous cell carcinoma cell line; T24, urinary bladder cancer; HeLa S3, uterine cervix cancer, MCF-7, breast cancer; SW-620, colon cancer; A172, human glioblastoma cell line; HEK293T, human embryonic kidney cell line; U20S, human bone osteosarcoma cells; PC12, phaeochromocytoma cell line; HPCs, hematopoietic progenitor cells; GBM, glioblastoma.

Several proteins involved in pro-survival and proliferative signaling cascades, such as EGFR, Ras, p21, protein kinase C (PKC) proteins, Myc and HER2 (ERBB2), have been found to be asymmetrically divided between sister cells in cancer (Cusulin et al., 2015; Czerniak et al., 1992). In proliferative cancer cells, the expression of such proteins is more heterogeneous in the G1 cell cycle phase than in S and G2/M. This variability might, at least in part, be due to the uneven distribution of those proteins during cell division. The duration of G0–G1 before the next mitosis is longer in sister cells that inherit lower expression of these proteins (Czerniak et al., 1992). Because cells that spend less time in interphase tend to have larger progenies, the asymmetric inheritance of pro-proliferative signaling proteins likely impacts cancer cell fitness (Lange et al., 2009).

Asymmetric division of organelles

ACD can target old or malfunctioning cellular components to one cell, and new, better-functioning components to the other cell. This occurs under physiological conditions in multiple organisms, from prokaryotes to multicellular eukaryotes (Betschinger and Knoblich, 2004; Chao et al., 2016), and is essential for maintaining cell fitness (Knoblich, 2001; Lerit et al., 2013). *Escherichia coli* cells that inherit more protein aggregates have decreased proliferative growth rates (Lindner et al., 2008). Similarly, in *Saccharomyces cerevisiae*, ACD occurs by targeting younger structures and organelles to the daughter cell, which thus inherits a higher level of fitness than its mother (Vevea et al., 2014). In yeast, the replicative life span (defined as the number of times a cell can divide before senescence) is used as a measure of aging. After mitosis, mother-and-daughter cells age asymmetrically, with aged mother cells budding to generate young daughter cells with full replicative potential. Cellular components retained in the mother cell that are aging determinants include extrachromosomal ribosomal DNA circles (Sinclair and Guarente, 1997) and protein aggregates containing damaged or unfolded proteins (Hashimshony et al., 2012; Higuchi-Sanabria et al., 2014), as well as malfunctioning organelles including vacuoles (Hughes and Gottschling, 2012) and mitochondria (Pernice et al., 2018).

Normal stem cells can also target damaged organelles to the daughter cell that is destined to differentiate, increasing the fitness of the daughter stem cell (Aguilaniu et al., 2003; Bufalino and van der Kooy, 2014; Katajisto et al., 2015). Hematopoietic stem cells (HSCs) spend most of their lives in a quiescent state; however, they reactivate the cell cycle in response to injury and replenish blood through differentiation into all blood cell lineages. During mitosis, lysosomes, autophagosomes and mitophagosomes are asymmetrically inherited into HSC daughter cells. The distribution of organelles predicts future asymmetries in metabolism, translational activation and cell fate in sister cells and their subsequent offspring (Loeffler et al., 2019). Interestingly, daughter cells with low levels of lysosomes differentiate without inducing specific blood lineage choices, whereas daughter cells with high levels of lysosomes maintain HSC quiescence and potency as a result of repression of lysosomal activation, enlargement of lysosomes and suppression of glucose uptake (Liang et al., 2020; Qiu et al., 2021).

In human mammary stem cells, asymmetric segregation of mitochondria is key for maintaining the stemness of one daughter cell. One study using fluorescent probes to discriminate between aged and young mitochondria has shown that old mitochondria were asymmetrically segregated after cell division even though daughter cells received the same amount of mitochondrial content. Prior to cell division, old mitochondria were mainly localized around the nucleus of the mother cell whereas younger mitochondria were dispersed throughout the cytoplasm (Katajisto et al., 2015). The cells that received more aged mitochondria showed flat, adherent, non-stem-like morphology and formed fewer mammospheres compared to the sisters that received more young mitochondria (Katajisto et al., 2015). These findings suggest that the asymmetric distribution of old mitochondria is a mechanism by which stem cells direct one cell to stemness and the other one to differentiation. Similarly, ACD has been observed in liver CSCs, in which daughter cells that receive fewer healthy mitochondria lose their stemness, whereas those that receive fewer dysfunctional mitochondria maintain it (Liang et al., 2020; Qiu et al., 2021). Suppressing asymmetric distribution of mitochondria in liver CSCs depletes the CSC pool and decreases their tumor-initiating capacity (Wei et al., 2023), highlighting the significance of ACD in cancer biology.

The higher fitness of these stem-like cells that inherit more ‘healthy’ organelles is likely one of the underlying reasons for the impact of ACD on the global fitness of the tumor, as the death of less-fit cells increases the average fitness of the cancer cell population. Whether additional cell components show asymmetry based on age or function during cell division is an open question that deserves close attention, especially in cancer research, as this could have a strong impact in the overall fitness of the cell population. Another major unanswered question is whether the asymmetric partitioning of cell components in cancer cell division is always accomplished by an active mechanism or if in some instances this happens stochastically. Furthermore, it is unknown whether ACD is exclusive to cells which express markers of stem cells.

Asymmetric division of phenotypes in cancer cells and ITH

Asymmetric segregation of cell components can elicit diverse effects on different cellular phenotypes. Some phenotypes classically linked to ACD during development and tissue homeostasis, such as cell fate, epithelial-to-mesenchymal transition (EMT) and cell fitness, are also highly relevant for cancer biology and therapeutics (Fig. 1B). We will next highlight phenotypic asymmetries associated with ACD in cancer and discuss how they can give rise to ITH. Table 2 lists studies that have shown asymmetric inheritance of such phenotypes in cancer cells with or without CSC markers.

Differences in cell size and localization

During development, ACD provides a mechanism for placing specific cell types at defined positions that determine cell fate and promote tissue differentiation. In *Caenorhabditis elegans*, for example, asymmetric segregation of the protease-activated receptor (PAR) complex during the first division of the zygote is responsible for cell size asymmetry and segregation of cell fate determinants (Cheeks et al., 2004). In the same way, asymmetric localization of NUMB, Miranda and Prospero proteins in the basal cortex of neuroblasts directs cells to divide asymmetrically along the apical–basal axis, giving rise to a small basal and a larger apical daughter cell during the development of the *Drosophila* nervous system (Hirata et al., 1995; Knoblich et al., 1995; Spana and Doe, 1995; Tirasophon et al., 1998). The larger apical daughter maintains neuroblast features and continues to divide several more times, whereas the smaller basal daughter cell only divides once more into two neurons (Knoblich, 2001). Thus, ACD can produce differences in cell size and spatial localization which determine future phenotypes of daughter cells.

Table 2. ACD of phenotypes or features in cancer cells

Phenotype or feature	CSC marker	Cell line or source	Main results	Reference
Cell size	CD133 and CD44	Polyploid giant cancer cells (PGCCs) of HEY and MDA-MB-231	PGCCs showed ACD via budding and bursting, producing cells of different sizes.	Zhang et al., 2014
EGFR, p75NTR (also known as TNR16 or NGFR) and self-renewal	CD133	Glioblastoma stem cells	EGFR and p75NTR were co-enriched in one of the daughter cells, favoring self-renewal capacity.	Hitomi et al., 2021
ERK, DNA damage, nuclear morphology	NA	A172 cells	Phenotypes related to fitness, such as ERK activity, DNA damage and nuclear morphology were asymmetric at mitosis or became asymmetric over the course of one cell cycle.	Buss et al., 2023
SOX2 and cell size	SOX2	OSCC (oral squamous cell carcinoma cell line)	Asymmetric distribution of SOX2 in ~25% of mitotic events; 40% of asymmetric daughter cells showed size differences.	Kaseb et al., 2016
Cell size and chromosome distribution	CD133	GBM primary culture and neural stem cell cultures	CD133+ cells divide by budding, producing daughter cells of different sizes with asymmetries in the distribution of chromosomes.	Jiang et al., 2015
Cell size	NA	Human cervical carcinoma (HeLa)	Abnormal multi-daughter division was induced by increasing confinement and substrate stiffness.	Tse et al., 2012
Chromosome alignment and cell size	NA	LNCaP and HeLa cells	Increase of asymmetric divisions (mostly 3 or 4 daughter cells) after treatment with a microtubule inhibitor.	Levrier et al., 2018
Fitness (number of daughter cells)	NA	LNCaP, PC-3 (prostate cancer) cells and HeLa	Treatment with a microtubule inhibitor induces severe mitotic spindle defects and asymmetric cell divisions, leading to mitotic catastrophe accompanied by apoptosis.	Levrier et al., 2017
Spindle division and organization	NA	HEK293 and H929 cells	The combination of *TP53* knockout and *NEK2* overexpression induces asymmetric spindle division *in vitro* and *in vivo*.	Feng et al., 2022
Mitotic spindle	NA	Colorectal cancer cell lines (HCT116)	A robust causal relationship between increased mitotic microtubule polymerization rates and asymmetric monopolar spindle formation.	Stolz et al., 2015
DNA content	NA	Human colon carcinoma (HCT116) tetraploid tumor cells	Tetraploid cells divide asymmetrically after a shorter mitotic arrest and both daughter cells eventually succumb to apoptosis.	Rello-Varona et al., 2009
Chromosome distribution	NA	Colorectal cancer cell lines (HCT116)	HCT 116 cells that were cultured in the presence of Mps-BAY1 or Mps-BAY2a exhibited a major disorganization of mitoses and asymmetric chromosome distributions.	Jemaà et al., 2013
Centrosome	NA	DT40 B-lymphoma cell line	Multi-polar mitoses are frequently resolved by asymmetric cell divisions causing unequal segregation of genetic material and cell death in one or both daughter cells.	Robinson et al., 2007

NA, not assessed.

Differences in cell fate

The maintenance of small populations of dividing stem cells in adult tissues is considered a central strategy for minimizing the total number of cell divisions and consequently errors in DNA synthesis (Tomasetti and Vogelstein, 2015). In this sense, ACD of cell fate is important in controlling tissue homeostasis and preventing carcinogenesis (Mannino et al., 2022; Simons and Clevers, 2011). However, in other contexts, ACD elicits pro-tumor effects, especially by contributing to the generation of ITH, which has recently been highlighted as a hallmark of cancer (Hanahan, 2022; Guo et al., 2019; Torres et al., 2016). Using single-cell RNA sequencing (scRNA-seq) and functional validation, Chao and colleagues have recently shown that ACD of colorectal CSCs promotes the establishment of ITH in xenografts. Colorectal CSC-derived tumors contained seven cell subtypes, which dynamically changed during xenograft progression. Three functionally distinct cell subtypes were generated by ACD at an early xenograft stage, whereas one subtype emerged later and was chemoresistant and highly invasive (Chao et al., 2023). By targeting the regulators that control the generation of these cell subtypes, the authors were able to change the CSC-derived tumor composition and progression (Chao et al., 2023), highlighting the importance of both ACD as a pro-tumoral agent and its contribution to intratumoral phenotypic heterogeneity in cancer progression.

One way of evaluating the existence of ACD is by analyzing the heterogeneity in colonies formed from a single cell. If all divisions in a colony are symmetric with regards to a given feature, then all cells should have the same quantity of this feature. For several features relevant in cancer biology, such as progression through the cell cycle, quantity of DNA double strand breaks and level of ERK and/or MAPK (ERK/MAPK) signaling, colonies become as heterogeneous as randomly grouped cells from the same population within a few divisions, indicating a high proportion of ACD (Lenz et al., 2021). In glioma cells, the proportion of divisions showing asymmetries in ERK/MAPK activity and intermitotic time was directly measured as ∼25% (Buss et al., 2023). Migration speed, a relevant feature for cancer invasion and metastasis, showed a high proportion of asymmetric phenotypic inheritance in glioma and breast cancer cells, with sister cells behaving as differently as unrelated cells (Tamborindeguy et al., 2023).

Differences in cell fitness

ACD of cell fitness can only be inferred by cell tracking (Wu et al., 2007) or by lineage tracing strategies (Yang et al., 2022), in which the actual number of descendants of two daughter cells are quantified after sufficient time to allow several cell divisions. In pheochromocytoma, daughter cells that inherit inclusion bodies associated with damaged proteins have a longer cell cycle and consequently decreased proliferation rates and fitness (Bufalino and van der Kooy, 2014). In leukemia cells, knockout of Cdc42, a protein that regulates division symmetry and cell cycle progression, drastically reduces the polarity of these cells, thus reducing directional migration, colony formation and cellular differentiation. Xenographic tumor fitness is reduced with silencing of Cdc42, but it is difficult to attribute this reduction in fitness only to the reduction in ACD, as Cdc42 has several functions (Mizukawa et al., 2017). Expression of oncoproteins, such as the fusion proteins BCR–ABL and NUP98–HOXA9, change the rates of ACD, suggesting that part of the roles of these oncoproteins relates to the modulation of the ACD rate (Wu et al., 2007).

Fitness heterogeneity in cancer can be an important barrier to therapy. Most currently available chemotherapies kill only a fraction of cells within a population at any given time, a phenomenon called fractional killing (Inde et al., 2020). Because cancer cells have dynamic fitness that fluctuates over a few days, the survival of only a few cells from a tolerant phenotypic region with high fitness can repopulate a tumor (Lenz et al., 2022). Evidence for the epigenetic basis of phenotypic heterogeneity comes from a recent study demonstrating a reduction in heterogeneity mediated by the inhibition of DNA methyltransferases and histone deacetylases (Lenz et al., 2021). In fact, pre-treatment of glioblastoma cells with epigenetic modulators reduced fractional killing by the alkylating agent temozolomide, indicating that epigenetic mechanisms are involved in generating heterogeneity in the tolerance to temozolomide (Lenz et al., 2021).

Proliferative variability resulting from ACD might also contribute to tumor heterogeneity and affect treatment outcomes. Highly proliferative cells are more affected by most cancer treatments, whereas cells with lower proliferative rates or dormant cells are typically less sensitive to these treatments (Sosa et al., 2015). Polyploid giant cancer cells (PGCCs) are dormant cells found in different tumor types; they express both normal and CSC markers, and under certain conditions are able to divide asymmetrically by budding, generating daughter cells of different sizes and proliferative capacity (Zhang et al., 2014). PGCCs-derived tumors have increased expression of CSC markers and become more resistant to chemotherapy treatment when compared to the original tumor (Jiang et al., 2015; Zhang et al., 2014).

In glioblastoma cells, proliferative phenotypes that influence cell fitness, such as ERK/MAPK signaling activity, were found to be asymmetric at mitosis or to become asymmetric over the course of the cell cycle (Buss et al., 2023). ERK/MAPK is a signaling pathway classically known to regulate cell proliferation, growth and survival (Lavoie et al., 2020), and has a direct impact on fitness phenotype. In a glioma cell line, ERK inhibition (ERK1/2, also known as MAPK3 and MAPK1, respectively) in the mother cell produced daughter cells with differences in intermitotic time, suggesting that ERK/MAPK is involved in ACD of proliferative variability (Buss et al., 2023). In this way, ACD events can be an important source of heterogeneity in cancer cells, especially in regard to phenotypes affecting the cell cycle and proliferative signaling that will impact fitness.

Evidence shows that cancer cells originating from ACD events perform new rounds of asymmetric divisions during the generation of daughter cells, suggesting that ACD is a behavior that can be transmitted to the daughter cells (Buss et al., 2023; Levrier et al., 2018; Tse et al., 2012). We recently reported that cells that received ERK/MAPK activity asymmetrically at mitosis, generate daughter cells that again distribute ERK/MAPK asymmetrically in subsequent ACDs (Buss et al., 2023). Both sister cells with low and high ERK activity were able to divide asymmetrically, suggesting that the asymmetry is not controlled by the level of ERK activity (Buss et al., 2023).

Despite compelling evidence from *in vitro* studies that ACD contributes to phenotypic heterogeneity in cancer cell populations, it is still unclear how often ACD occurs in tumors *in vivo.* Assessing the symmetry of fitness in actual tumors remains a difficult task. A recent study from Yang and colleagues employed a lineage tracing strategy using continuous CRISPR-Cas9 DNA scar formation linked to scRNA-seq in a Kras;p53-driven mouse lung cancer model. By generating a DNA scar on average at every second generation, it was possible to reconstruct a lineage tree of the cancer cells. If all divisions were to be symmetric in relation to fitness, the tree would be symmetric, with all branches producing the same number of descendants. However, ∼60% of the tumors had a dominant lineage branch representing close to 50% of the cells in the tumor, indicating asymmetries among the branches and ACD of cell fitness. Linking cell tracing to scRNA-seq indicates that the dynamics cell states are more consistent with the epigenetic rather than genetic origin of this expansion. Even in the 14% of the tumors with no dominant subpopulation, the lineage tree was far from symmetric, indicating that asymmetric inheritance of fitness is the rule rather than the exception in cancer (Yang et al., 2022).

Extrinsic drivers of ACD

As mentioned above, ACD in cancer cells is associated with CSCs, which have retained stem cell markers and the capacity to divide asymmetrically (Beckmann et al., 2007; Izumi and Kaneko, 2012). However, ACDs in cancer cells can also be induced by interaction with the tumor microenvironment (TME). Glioblastoma stem-like cells in culture, for example, showed increased incidence of ACD when epidermal growth factor (EGF) was removed from the culture medium; this increased tumor heterogeneity and produced cells with high stemness (Lathia et al., 2011). Furthermore, the frequency of asymmetric segregation of DNA template in lung cancer cells *in vitro* positively correlated with cell density and was modulated by environmental changes, including serum deprivation and hypoxia (Pine et al., 2010), suggesting that adverse TME conditions have a substantial influence on the occurrence of ACD in cancer. The idea that changes in the TME and microenvironmental stressors can modulate ACD in cancer raises the possibility that ACD is a mechanism by which tumor cells adapt and survive under unfavorable conditions, such as hypoxia, nutrient deprivation, confined spaces and even therapy. In this context, changes in the microenvironment during tumor progression or as a result of treatment might give rise to heterogeneity in cancer cells by promoting the acquisition of stem-like phenotypes and increasing the incidence of ACD.

Three-dimensional (3D) cultures offer a superior experimental model for studying the influence of the TME on the occurrence of ACD in cancer cells, as they more accurately replicate the adverse environmental factors associated with hypoxia and confinement. For example, HeLa cells mechanically confined in 3D cultures showed asymmetric inheritance of multiple phenotypes, including longer cell cycles, unevenly sized daughter cells and anomalous multi-daughter mitosis events. Surprisingly, cells under the most confining conditions had a 50-fold higher frequency of divisions producing more than two daughter cell structures compared to cells in 2D environments, and the daughter cells resulting from these multipolar divisions were viable after cytokinesis (Tse et al., 2012). In a recent *in vitro* morphogenesis study using several cancer-derived and non-cancer cell lines, Chen and colleagues demonstrated that a compression gradient induced by the interaction of multiple cell layers triggered a reorientation of cell division from symmetric to asymmetric, ultimately resulting in tissue stratification. The SCD-to-ACD switch was induced by changes in the subcellular localization of NuMA1, which caused one daughter cell to relocate to the topmost layer of the cell sheet while the other remained in the central region. The cells in the central region had a significantly higher level of ACD when compared to their sisters located in the outer layers as a result of higher compression levels (Chen et al., 2022).

Antitumor therapy can also be considered a driver of ACD because it affects the balance between SCD and ACD in cancer (Katsuki et al., 2008; Lai et al., 2016; Mittal et al., 2017; Qu et al., 2016, 2017). Lai and colleagues have shown that a combination of rapamycin, a small-molecule that inhibits mammalian target of rapamycin (mTOR) signaling, and low-dose radiation induced the ACD of triple-negative breast CSCs (Lai et al., 2016). Similarly, axitinib, a small molecule that inhibits Wnt signaling, induces asymmetric inheritance of Wnt signaling activity, β-catenin and nonrandom DNA template segregation in adenocarcinoma cancer cells. ACD was rarely observed in untreated adenocarcinoma cells (Qu et al., 2016, 2017), suggesting a possible reactivation of stem cell phenotypes after treatment, or the induction of ACD in non-CSCs. As already mentioned, phenotypic ITH is thought to allow the survival of a small fraction of cells after treatment that are capable of regrowing the tumor. Docetaxel, a chemotherapeutic largely used to treat breast, lung and prostate cancers, was found to induce the emergence of PGCCs that escaped from mitotic arrest and underwent mitotic slippage, generating mononucleated daughter cells via ACD or budding. These daughter cells derived from PGCCs had increased pro-survival signaling, were positive for the stem marker CD44 and were resistant to docetaxel chemotherapy. These findings highlight the role of ACD in PGCCs in the generation of phenotypic heterogeneity that can lead to clinical relapse and chemoresistance (Mittal et al., 2017). Overall, the evidence suggests that reactivation of ACD during tumor development and therapy is a mechanism by which tumor cells increase phenotypic heterogeneity in order to adapt and survive to microenvironmental and therapy challenges.

Conclusion and open questions

Taken together, it is reasonable to suggest that ACD in the context of cancer is implicated in various pathological features that contribute to increased tumor heterogeneity, especially in terms of cell fitness. The tendency to undergo ACD can be inherited by daughter cells and drive resistance to therapy in CSCs. However, ACD is not exclusively associated with cancer cells expressing stem cell markers, which questions the assumption that the impact of ACD is linked exclusively to CSCs. Notwithstanding, asymmetric inheritance of cell components and consequently phenotypes contribute to the mechanisms responsible for generating heterogeneity in cancer cells, thus driving adaptation to stress and tolerance to therapy. Despite the recognition of its importance, there is not currently a clear avenue toward targeting ACD to reduce the generation of ITH. One way forward is to better understand the mechanisms that control the decision of stem cells to perform ACD, so that these mechanisms can be rationally modulated to reduce ACD in cancer.

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Competing interests

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