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Differentiation of Somatic Cells in Multicellular Organisms

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Abstract

Multicellular organisms employ intricate gene regulatory networks (GRNs) to orchestrate cell fate decisions, yet the precise regulatory mechanisms that govern transcription factors (TFs) within these networks remain exceptionally complex. A long-standing question in this field pertains to how these intricate interactions synergistically contribute to decision-making processes. To gain a comprehensive understanding of the role of regulatory logic in cell fate determinations, we developed a logical model of GRNs and examined its behavior under two distinct driving forces—one governed by stochastic noise and the other by deterministic signaling. Under noise-driven conditions, we identified a correlation between fate biasing, regulatory logic, and noise profile dynamics. In the signal-driven mode, we established a connection between regulatory logic and the trade-off between accuracy and progression speed, revealing distinct reprogramming trajectories influenced by specific logical motifs. Through differentiation studies, we characterized a unique priming stage that is dependent on regulatory logic, employing decision landscapes for analysis. Finally, we applied our findings to elucidate three biological cases: hematopoiesis, embryogenesis, and transdifferentiation. Orthogonally to classical expression profile analysis, we leveraged noise pattern recognition to construct GRNs corresponding to fate transitions. Our research presents a generalizable framework for downstream investigations of fate determination and offers a practical approach for the taxonomy of cell fate decisions.

Keywords: Protein Aggregation, Heat Shock Proteins, Molecular Chaperones, Asymmetric Cell Division, Proteostasis, Replicative Aging

Introduction

Induction is commonly defined as an effect that arises in response to an external influence. Thus, when a factor present in the cellular microenvironment or surrounding the nucleus induces differentiation in a cell to some extent, this differentiation is attributed to induction.

Differentiation, except for the earliest stages of embryonic development, is typically considered a consequence of induction—that is, the emergence of specific cellular effects under the influence of the surrounding microenvironment. These effects, mediated through the cytoplasm, lead to the expression of various genes in cells that are competent to respond to transcription factors (inducers).

To determine the types of inducers capable of initiating differentiation, it is necessary to investigate environmental factors that can modulate gene expression within a cell in a way that prompts the synthesis of novel proteins. A demonstrative example was discovered through experiments on bacteria, which, unlike eukaryotes, do not undergo differentiation. These experiments illustrated how an external inducer can suppress the activity of one gene while simultaneously activating another. Since this suppression-activation process is reversible, it is classified as modulation rather than differentiation.

Bacteria produce both constitutive and inducible enzymes. Constitutive enzymes participate in fundamental metabolic processes and their gene expression does not require environmental cues. In contrast, inducible enzymes are synthesized in very small, trace amounts. For example, Escherichia coli primarily metabolizes glucose. However, in the absence of glucose, the bacterium can utilize lactose after converting it into glucose. This conversion necessitates the enzyme β-galactosidase, which is present only in minimal amounts. When a high concentration of lactose becomes available in the environment, the synthesis of β-galactosidase is significantly upregulated. The influence of the substrate on gene activation is indirect, occurring through a complex system of suppressor genes and operator genes. Regardless of how intricate the activation or deactivation mechanisms of specific genes may be in either prokaryotic or eukaryotic cells, including those of multicellular organisms, modulation should not be mistaken for irreversible differentiation. The term "differentiation" should no longer be applied to modulation, as true differentiation is typically irreversible in normal cells and is associated with structural changes in genetic material. Such changes may only be reversible in sibling cells.

Asymmetric Division and Differentiation

Asymmetric cell division (ACD) represents a highly conserved mechanism that has evolved to generate cellular diversity. The fundamental principle of ACD is the establishment of distinct fates among daughter cells (sibling cells) through mitosis-associated mechanisms. Asymmetric fate determination can be influenced by external signaling cues received by the cell. Alternatively, asymmetric inheritance of intrinsic fate determinants—such as specific proteins or RNAs—can directly drive differential cell fate outcomes. The latter mechanism was first demonstrated over a century ago by Edwin Conklin, who observed that during the early

cleavage stages of Ascidiacea embryos, yellow cytoplasm was asymmetrically partitioned to specify muscle cell fate (Conklin, 1905).

Beyond macromolecules, organelles such as centrosomes, midbodies, mitochondria, the endoplasmic reticulum (ER), and lysosomes have been reported to undergo asymmetric inheritance. Interestingly, the asymmetric distribution of organelles appears to be the norm rather than the exception, yet its precise role in establishing differential cell fates remains unclear in many cases.

Asymmetry and Selective Inheritance of RNAs and Proteins by Sibling Cells

Cell fate decisions can be influenced by the asymmetric distribution of molecular determinants, such as RNA species or proteins. For instance, messenger RNAs (mRNAs) segregated into one sibling cell can rapidly translate into proteins that drive distinct cellular behaviors. Alternatively, regulatory RNAs and proteins can modulate gene expression, protein localization, and cellular function. Often, polarized distribution precedes asymmetric segregation.

One of the earliest recorded examples of asymmetric RNA localization involved actin isoforms in early Styela plicata embryos, identified via in situ hybridization (Jeffery et al., 1983). More recently, a high-resolution fluorescent in situ hybridization (FISH) analysis of mRNA dynamics during early Drosophila melanogaster development revealed that 71% of genes expressed in this time window exhibit distinct subcellular localization patterns. Notably, many of these genes show polarized distribution, primarily localizing to either the apical or basal cortex of the cell (Lécuyer et al., 2007). Subcellular localization of various RNA species, including mRNAs, long non-coding RNAs, and circular RNAs, has also been identified using a combination of cell fractionation and RNA sequencing in human and Drosophila cells (Bouvrette et al., 2017). Although this study did not explicitly analyze polarized RNA distribution, it clearly demonstrated that most RNAs are localized to specific cellular compartments.

A compelling example of how asymmetric RNA localization drives cell fate determination was demonstrated in spiral cleavage. In Ilyanassa obsoleta, mRNAs of developmental patterning genes Eve, DPP, and Tld localize to centrosomes during early cleavage cycles and subsequently segregate into one daughter cell during division (Lambert and Nagy, 2002). Centrosomal RNA localization appears to be a dominant mechanism for embryonic patterning in this system, as similar observations have been made for multiple other mRNAs (Kingsley et al., 2007). These RNAs exhibit two distinct intracellular movements: initial attraction to interphase centrosomes, likely via minus-end-directed transport, followed by cortical relocalization into a region inherited exclusively by one daughter cell. Microtubule integrity is essential for centrosomal RNA accumulation, whereas actin filaments mediate subsequent cortical relocalization (Lambert and Nagy, 2002).

Further mechanistic and functional insights into polarized RNA distribution and segregation have emerged from studies of asymmetrically dividing Drosophila neural stem cells, known as neuroblasts. Neuroblasts divide asymmetrically, yielding a self-renewing neuroblast and a differentiating ganglion mother cell (GMC) (Gallaud et al., 2017). The mRNA of the transcription

factor Prospero (Pros; Prox1 in vertebrates) localizes apically during interphase before shifting to the basal cortex in mitosis (Schuldt et al., 1998). This localization is mediated by Inscuteable (Insc) and the RNA-binding protein Staufen (STAU1/2 in vertebrates), which binds the Prospero 3′ untranslated region (Li et al., 1997). These findings highlight the fundamental importance of RNA and protein asymmetry in cell fate determination across multiple biological systems.

Other types of RNA also exhibit highly specific subcellular localization patterns and perform distinct functions within different cellular compartments. For example, extensive research has revealed that the long non-coding RNA cherub exhibits a strikingly asymmetric distribution within mitotic larval neuroblasts, where it localizes predominantly to the basal cortex and segregates asymmetrically into the immature neuronal progenitor cell (Landskron et al., 2018). This specific localization of cherub is critically dependent on the RNA-binding protein Staufen, which facilitates its basal positioning. Furthermore, cherub establishes an intricate molecular interplay between Staufen and another RNA-binding protein, Syncrip (Syp; known as heterogeneous nuclear ribonucleoprotein R, or HNRNPR, in humans). Interestingly, despite its well-defined asymmetric segregation, cherub is not required for normal asymmetric cell division (ACD) or standard developmental processes. However, it plays a pivotal role in tumor progression within mutant neural tissue carrying brain tumor mutations (brat ; homologous to Trim2, Trim3, and Trim32 in vertebrates). Specifically, cherub interferes with the normal temporal progression of neuroblast divisions, allowing tumor cells to evade differentiation constraints and sustain indefinite proliferation.

Long non-coding RNAs are also instrumental in the establishment of cell fate during early mammalian embryogenesis. In murine embryos, the long non-coding RNA lincGET (Gm45011) has been found to display a transient yet highly asymmetric expression pattern during the critical two- to four-cell transition stage of pre-implantation development (Wang et al., 2018). Functionally, lincGET physically interacts with coactivator-associated arginine methyltransferase 1 (CARM1), directing its nuclear localization. This molecular interaction ultimately biases blastomeres toward an inner cell mass (ICM) fate by promoting the activation of ICM-specific genes. Previous models suggested that lineage segregation occurs at later developmental stages and was closely linked to the expression of the transcription factor CDX2, whose mRNA transcripts localize apically at the eight-cell stage and are inherited asymmetrically, effectively distinguishing pluripotent cells from differentiating ones (Skamagki et al., 2013).

These examples underscore the critical role of RNA localization in establishing cellular asymmetries, providing a mechanistic basis for the asymmetric segregation of specific transcripts. However, many mechanistic aspects of RNA localization dynamics, as well as the precise cellular and developmental functions of localized RNA species, remain to be elucidated. Beyond RNA, the polarized distribution of proteins and their asymmetric segregation have been extensively studied in Drosophila neuroblasts and C. elegans embryos (Loyer and Januschke, 2020).

One of the earliest and most extensively characterized protein families regulating asymmetric cell division is the partitioning-defective (PAR) polarity proteins. Initially discovered in C. elegans

as key determinants of zygotic polarization—forming two opposing protein domains within the embryo (Kemphues et al., 1988)—PAR proteins are now recognized as evolutionarily conserved regulators of apical-basal polarity in diverse organisms (Boxem and Heuvel, 2019). In Drosophila neuroblasts, apical-basal polarity is orchestrated by the PAR complex, consisting of Par-3 (BAZ), PAR-6, and atypical protein kinase C (aPKC), which collectively form an apical polarity cap. Notably, aPKC localization at the apical cortex is initiated during early prophase, where it first appears as discrete cortical foci, gradually expanding and coalescing into a crescent-shaped domain by metaphase before dispersing back into smaller cortical patches during telophase (Oon and Prehoda, 2019). The precise mechanism governing the initial recruitment of aPKC to the apical hemisphere remains unresolved, though subsequent crescent formation is dependent on cortical flow dynamics. A similar mechanism has been proposed for Par-3.

A recent study uncovered a novel interaction between the second PDZ domain of Par-3 and a highly conserved PDZ-binding motif (PBM) in aPKC (Holly et al., 2020). Par-3 is phosphorylated by the complete PAR complex, and this phosphorylation event induces the dissociation of Par-3's phosphorylation site from the aPKC kinase domain while preserving the Par-3 PDZ2-aPKC PBM interaction. This represents the first direct Par-3-aPKC interaction demonstrated to be essential for the cortical recruitment and polarization of aPKC in neuroblasts.

PAR complex activity is crucial for the proper localization of basal cell fate determinants such as Miranda and Numb, which segregate specifically into the ganglion mother cell (GMC) to direct neuronal differentiation. Miranda initially localizes to the apical interphase centrosome in embryonic neuroblasts (Mollinari et al., 2002) but adopts a uniform cortical distribution during interphase in larval neuroblasts (Sousa-Nunes et al., 2009). During metaphase, Miranda undergoes a dramatic shift, forming a basal cortical crescent (Matsuzaki et al., 1998). This basal localization is induced by aPKC-mediated phosphorylation, which actively excludes Miranda from the apical cortex (Atwood and Prehoda, 2009) and is further stabilized by the actomyosin cytoskeleton (Hannaford et al., 2018). Additionally, Miranda's phosphorylation state and subcellular localization are modulated by protein phosphatase 4 and its associated cofactors, including phosphotyrosyl phosphatase activator (PTPA) (Zhang et al., 2015). Functionally, Miranda serves as a cargo protein, transporting translational inhibitors such as Brat and Prospero (Pros). Within GMCs, Prospero represses genes associated with self-renewal—including stem cell fate and cell cycle regulators—while simultaneously activating terminal differentiation programs (Choksi et al., 2006).

Intriguingly, multiple RNA transcripts and their corresponding protein products exhibit coordinated localization within Drosophila neuroblasts. However, it remains unclear whether the asymmetric positioning of mRNA correlates with localized protein translation, necessitating further investigation into the functional significance of RNA localization in this context.

Cytoskeleton asymmetry

Centrosomal mRNA localization suggests molecular and/or structural asymmetries between centrosomes within the same cell. A striking example of this phenomenon occurs in Drosophila neuroblasts, where centrosomes exhibit distinct microtubule-organizing center (MTOC) activity profiles, particularly during interphase. Centrosomes comprise two centrioles encased within a pericentriolar matrix (PCM), which is essential for MTOC function. During each cell cycle, centrioles undergo replication, whereby a “daughter” centriole forms orthogonally adjacent to the older “mother” centriole. As the cell cycle progresses, the centrioles disengage, forming two mature MTOCs that establish the bipolar mitotic spindle (Conduit et al., 2015). This replication cycle inherently introduces an age asymmetry between centrioles, which has been corroborated by molecular markers (Jakobsen et al., 2011; Januschke et al., 2011). In neuroblasts, the daughter centriole-containing centrosome maintains active microtubule nucleation throughout interphase, whereas the mother centriole-containing centrosome suppresses MTOC activity upon neuroblast entry into interphase. This differential MTOC activity helps align the mitotic spindle along the neuroblast’s apical-basal polarity axis, as the active MTOC remains anchored to the apical cortex. The mother centriole-containing centrosome is inactivated through PCM shedding, leading to its displacement from the apical cortex. By prophase, both centrosomes reaccumulate PCM components and regain microtubule nucleation capacity (Lerit and Rusan, 2013). This stereotyped MTOC behavior results in biased centrosome segregation, where the apical centrosome, containing the younger daughter centriole, is retained in the self-renewing neuroblast, while the mother centriole is inherited by the differentiating GMC.

Similar biased centrosome inheritance patterns have been observed in Drosophila germline stem cells (Salzmann et al., 2014), mouse neural stem cells (Wang et al., 2009), and budding yeast (Pereira et al., 2001).

In male germline stem cells (GSCs) of Drosophila, the differential activity of the microtubule-organizing center (MTOC) is strongly associated with the maturity of the centrosome. Specifically, the older centrosome, which contains the maternal centriole, maintains the pericentriolar material (PCM) and MTOC activity, ensuring that it remains anchored near the stem cell niche (Yamashita et al., 2007). This asymmetric behavior of the centrosome plays a critical role in the maintenance of stem cell identity and division orientation. However, in Drosophila neuroblasts, cortical signaling pathways, particularly those mediated through the polarity protein Partner of inscuteable (Pins; known as LGN (Gpsm2) and AGS3 (Gpsm1) in vertebrates), significantly influence the asymmetric regulation of MTOC activity (Rebollo et al., 2007).

Similarly, in yeast, studies have shown that spatial signaling mechanisms, rather than the kinetic process of spindle pole body (SPB) maturation, are responsible for controlling the asymmetry in astral microtubule organization between pre-existing and newly formed SPBs (Lengefeld et al., 2017). The precise mechanisms by which such spatial signals exert control over differential MTOC activity remain unclear. However, research on Drosophila neuroblasts suggests that MTOC asymmetry can be regulated by the mitotic kinase Polo (Plk1 in vertebrates). Polo has been found to phosphorylate various PCM proteins, an essential step for sustaining MTOC

activity (Feng et al., 2017). Furthermore, the maintenance of Polo/Plk1 at the daughter centriole is crucial for ensuring the integrity of PCM and its associated MTOC function (Conduit and Raff, 2010).

While the apically positioned daughter centriole retains Polo/Plk1, thereby preserving MTOC activity, the maternal centriole acts oppositely by suppressing Polo/Plk1 and depleting its associated PCM components, resulting in the loss of MTOC activity. Consequently, this causes the maternal centriole to detach from the apical cortex of the neuroblast (Ramdas Nair et al., 2016). Interestingly, Polo-like kinase 4 (Plk4; also referred to as SAK), a pivotal regulator of centriole duplication, has also been implicated in establishing centriole asymmetry and the associated differential MTOC activity. Plk4 phosphorylates Spd-2, a process that triggers basal-like centriole behavior (Gambarotto et al., 2019). Notably, this asymmetric MTOC activity in neuroblasts is transient and disappears during mitosis, when the centrosome containing the maternal centriole initiates maturation, thereby re-establishing a second functional MTOC.

In yeast, the differential dynamics of microtubule growth have been attributed to the kinesin Kip2, which is selectively recruited to the older SPB (Chen et al., 2019). Kip2 plays a crucial role in preventing microtubule catastrophe and promoting microtubule extension (Hibbel et al., 2015). Phosphorylation of Kip2 is critical in ensuring that microtubules do not bind randomly, initially restricting its activity to the minus-end. Thus, the recruitment of Kip2, which is regulated by Bub2 and Bfa (Bfa1), may account for the generation of longer astral microtubules emanating from the older SPB, owing to Kip2's ability to prevent microtubule catastrophe and support their elongation.

As MTOCs are fundamental to the formation of bipolar spindles, the asymmetric activity of MTOCs may also contribute to spindle asymmetry, which could have significant implications for the shape and size of sibling cells. The kinesin Klp10A, which acts as a microtubule-depolymerizing enzyme, is specifically localized to the centrosome of male GSCs in Drosophila. Loss of Klp10A results in abnormal elongation of the maternal centrosome in GSCs, leading to an abnormally large MTOC and an associated half-spindle, which, in turn, gives rise to an asymmetric mitotic spindle. Ultimately, this results in the division of GSCs into daughter cells of unequal size (Chen et al., 2016). Thus, Klp10A actively counteracts spindle asymmetry by preventing unequal formation of sibling cells.

Mutations in cell polarity proteins can also affect spindle asymmetry (Cai et al., 2003), though the underlying molecular mechanisms remain largely unexplored. Evidence for the role of centrosomal proteins in maintaining spindle symmetry has also been observed in human cells. For instance, the centrosomal coiled-coil domain-containing protein 61 (CCDC61) is essential for spindle assembly and chromosome alignment in cultured human cells; depletion of CCDC61 results in a loss of internal symmetry within spindle-associated microtubule tracks (Bärenz et al., 2018).

Spindle morphology must also be tightly regulated in acentrosomal cells, such as oocytes. In Drosophila oocytes, acentrosomal spindles are generally symmetrical, but loss of the kinesin-5

motor protein (Klp61F) leads to asymmetric bipolar spindles, where one half of the spindle contains a greater density of microtubules (Radford et al., 2016). Although the precise role of kinesin-5 in preventing asymmetric spindle formation remains unclear, simultaneous depletion of kinesin-6 (Subito) alongside Klp61F exacerbates the asymmetric spindle phenotype, suggesting that both kinesin-5 and kinesin-6 contribute to spindle symmetry in Drosophila oocytes.

Spindle asymmetry has been identified as a crucial regulator of Notch signaling in asymmetrically dividing sensory organ precursor (SOP) cells in Drosophila. In this system, Klp10A and its antagonist Patronin establish spindle asymmetry, which, in turn, directs the polarized mobility of endosomes, thereby mediating biased transport of Sara-containing endosomes into one sibling cell (Derivery et al., 2015). This polarized trafficking of Sara endosomes is an essential mechanism for facilitating asymmetric Notch/Delta signaling during SOP division in Drosophila (Coumailleau et al., 2009). Spindle asymmetry has also been proposed as a mechanism for biased chromosome segregation during meiosis, commonly referred to as meiotic drive (Kursel and Malik, 2018). This phenomenon has been demonstrated in mouse oocytes, which utilize CDC42 signaling from the cell cortex to regulate tubulin tyrosination, thereby establishing spindle asymmetry and promoting non-Mendelian segregation of bivalents (Akera et al., 2017).

What is the connection between spindle asymmetry and sibling cell size asymmetry? Studies on mutant Drosophila GSCs lacking Klp10A demonstrate that enhanced MTOC activity at the stem cell centrosome leads to asymmetric spindle formation and, consequently, the generation of daughter cells of unequal size, despite the fact that GSCs typically divide symmetrically in terms of size. Likewise, loss of the Drosophila polarity protein Pins, which influences MTOC activity during interphase and spindle asymmetry during mitosis (Yu et al., 2000), causes neuroblasts to divide into equal-sized daughter cells (Cabernard et al., 2010). However, whether size asymmetry is exclusively determined by spindle asymmetry remains uncertain.

Recent studies indicate that cortical signaling pathways can override intrinsic spindle asymmetry. For instance, Drosophila neuroblasts lacking Protein kinase N (Pkn; Pkn1-3 in vertebrates) exhibit transient defects in sibling cell size asymmetry during mitosis. Unlike wild-type neuroblasts, which generate a large apical neuroblast and a small ganglion mother cell (GMC), pkn mutant neuroblasts initially show a reduced apical domain and an expanded basal cortex in early anaphase (Tsankova et al., 2017). This transient inversion of asymmetry appears to be linked to altered localization of non-muscle myosin II (myosin). Further studies are required to fully understand these complex mechanisms.

A fundamental principle emerging from these studies is that cells employ multiple distinct mechanisms to establish asymmetry in the size of sibling cells (Roubinet and Cabernard, 2014). As previously mentioned, both centrosome-dependent and centrosome-independent mechanisms can result in asymmetric mitotic spindles, which in turn displace the cleavage furrow toward one side of the cell cortex. This displacement of the mitotic spindle under these conditions leads to physical asymmetric cell division (ACD) (Sallé et al., 2018). Similarly, in sea urchin embryos, ACD occurs to generate micromeres—small organizer cells that provide

inductive signals to neighboring cells crucial for gastrulation—at the vegetal poles of embryos during the transition from the 8-cell stage to the 16-cell stage. Micromeres are smaller than their macromere sibling cells and inherit the RNA helicase protein Vasa (Juliano et al., 2006). The polarity factor AGS is both necessary and sufficient for establishing this physical and molecular ACD. The AGS of sea urchins contains three GoLoco motifs, whereas the AGS of sea stars lacks GoLoco motif #1. Recent findings demonstrate that the expression of sea urchin AGS in sea star embryos is sufficient to induce physical ACDs (Poon et al., 2019). Additionally, a primary cortical force-generation mechanism responsible for such cortical pulling forces is evolutionarily conserved and comprises the Dynein-Dynactin complex, NuMA (Lin5 in C. elegans; Mud in Drosophila), and the Gαi complex (GOA-1, GPA-16 in C. elegans; Gαi in Drosophila) (Kiyomitsu, 2019). Cell shape, adhesion geometry, intercellular junctions, and mechanical tension are additional factors that dictate spindle orientation and positioning (van Leen et al., 2020). Lastly, as observed in Drosophila and C. elegans neuroblasts, measurable dynamic changes in the cell cortex during anaphase can induce asymmetry in sibling cell sizes. Intriguingly, recent studies in the developing chordate Ciona have revealed that different chordate blastomeres employ a combination of polarized mitotic spindle displacement, maternal cell shape, and post-anaphase mechanisms across various rounds of cell division to establish unequal sibling cell sizes (Winkley et al., 2019).

Another poorly described mechanism for generating sibling cells of unequal size is employed by many mollusks and certain species of annelid worms (Chen et al., 2006). These invertebrates generate two sibling cells of distinct sizes by forming and reintegrating a polar lobe. Polar lobes, also known as antipolar or yolk lobes, are transient vegetal protrusions that form during the first and second embryonic divisions, sequestering vegetal cytoplasm, which is subsequently inherited by CD and D blastomeres (Morgan, 1933). Most studies on polar lobe formation and resorption have been conducted in the snail I. obsoleta, revealing that both actin and myosin are essential for polar lobe formation and resorption (Hejnol and Pfannenstiel, 1998). Research using two closely related scallop species, Chlamys hastada and C. rubida, demonstrated that the region of the cell cortex designated for polar lobe sequestration is marked by enrichment of the Arp2/3 complex. Moreover, inhibition of Arp2/3 disrupts polar lobe formation and cytoplasmic partitioning into sibling cells, suggesting that Arp2/3 plays a functional role in specifying the cortical region that will be sequestered into the polar lobe (Toledo-Jacobo et al., 2019). The molecular mechanisms underpinning polar lobe formation remain largely unknown, but classical microsurgical experiments have shown that polar lobes play a pivotal role in cell fate determination (Render, 1989).

Much more could be learned about ACD by studying unconventional or emerging model systems such as snails and scallops; however, the current lack of molecular tools for investigating these species remains a limiting factor in understanding these processes.

Centrosome, Histone, and Chromosome Segregation Asymmetry

Epigenetic mechanisms (related to the cell nucleus) play a crucial role in specifying cell fate by modifying chromatin structure and regulating gene expression. Studies have demonstrated that during asymmetric division of male germline stem cells (GSCs) in Drosophila, pre-existing

canonical histones H3 and H4 are preferentially retained by the stem cell, whereas newly synthesized H3 and H4 are inherited by the differentiating daughter cell, known as the gonial blast (Wooten et al., 2019). In contrast, H2A and H2B are symmetrically distributed. Loss of H3T3P phosphorylation disrupts asymmetric H3 inheritance, leading to stem cell loss and the formation of early-stage germline tumors (Xie et al., 2015).

Spindle asymmetry and centromeric modifications bias chromatid segregation. In male GSCs of Drosophila, the mother centrosome generates an active microtubule-organizing center (MTOC) before the daughter centrosome. Asymmetry in nuclear envelope breakdown subsequently allows microtubules from the mother centrosome to attach to sister chromatids containing larger kinetochores. Sister centromeres are differentially enriched in proteins involved in centromere specification and kinetochore function. This results in preferential recognition and attachment of microtubules to asymmetric sister kinetochores and centromeres, ensuring that epigenetically distinct sister chromatids are asymmetrically partitioned in male GSCs (MT, microtubules).

Another form of epigenetic modification occurs at centromeres, which, along with kinetochore proteins, form microtubule attachment sites essential for accurate chromosome segregation. Centromeric chromatin lacks a specific DNA sequence but is epigenetically defined by the histone H3 variant CENP-A (CID in flies) (Allshire and Karpen, 2008). In Drosophila intestinal stem cells, previously synthesized CENP-A is preferentially retained by the stem cell, whereas differentiating progenitor cells are enriched with newly assembled CENP-A (García del Arco et al., 2018). The mechanisms and functional consequences of this biased CENP-A segregation remain to be elucidated. Similarly, CENP-A has been found to be asymmetrically enriched on the sister chromatid segregating into GSCs in male Drosophila testes. How this epigenetic modification influences chromatid segregation and potentially cell fate decisions remains an open question. Data, primarily from Drosophila GSC studies, suggest that the kinetochore protein Ndc80 is also asymmetrically localized, correlating with CENP-A enrichment. As mentioned earlier, the nuclear envelope specifically ruptures first on the presumptive GSC side, creating an opening for microtubules from the more active mother centrosome to penetrate and attach to chromatids exhibiting higher concentrations of Ndc80. This may, in turn, lead to biased chromatid segregation. This mechanism closely resembles the process observed in mouse oocytes, which also exhibit asymmetric microtubule attachment to kinetochore complexes, thereby biasing chromosome segregation (Akera et al., 2019). This "meiotic drive" in oocytes is determined by centromeric differences between homologous chromosomes, whereas "mitotic drive" occurs between genetically identical sister chromatids. Since sister centromeres are theoretically identical in sequence, CENP-A must be asymmetrically assembled via an as-yet-unknown mechanism (Wooten et al., 2019b), necessitating further research to uncover the molecular underpinnings of this event.

Asymmetric separation of protein aggregates and organelles

Protein aggregates arise when hydrophobic regions of multiple unfolded polypeptides adhere to one another, forming stable or semi-stable complexes. This phenomenon occurs when proteins lose their native conformation due to external stress factors, such as elevated temperatures, oxidative stress, or aging-related cellular deterioration. A crucial cellular mechanism for

mitigating these potentially harmful protein interactions involves the activity of small heat shock proteins (sHsp), which function as the first line of defense against irreversible protein aggregation. These molecular chaperones play a protective role by stabilizing misfolded or partially denatured proteins and preventing them from forming insoluble toxic aggregates.

For instance, when cells experience a heat shock, proteins that have lost their proper three-dimensional structure expose previously buried hydrophobic regions, which can lead to aberrant intermolecular interactions. Such interactions frequently result in the formation of cytotoxic, insoluble protein aggregates that disrupt normal cellular function. The association of small heat shock proteins with these unfolded or misfolded protein substrates serves to prevent their uncontrolled aggregation and accumulation. Additionally, this interaction facilitates the subsequent refolding and functional restoration of these proteins through the action of ATP-dependent chaperones, such as Hsp104p, which plays a pivotal role in protein disaggregation and reactivation (Liberek et al., 2008).

A particularly effective strategy for minimizing the accumulation of protein aggregates within a cellular population is asymmetric division, a process observed in certain unicellular organisms. A prime example of this occurs in budding yeast, where dividing cells restrict protein aggregates to the aging mother cell, ensuring that the newly formed daughter cell remains rejuvenated and free from toxic aggregates. This segregation mechanism contributes to the maintenance of cellular fitness across generations.

Hsp26p, a small heat shock chaperone, is specifically involved in the regulation of proteostasis and is known to associate with various aggregation-prone proteins (Cashikar et al., 2005). Under optimal growth conditions, the expression of Hsp26p remains low; however, it is dramatically upregulated in response to oxidative stress, heat shock, or nutrient depletion—conditions that drive cells into a stationary phase (Franzmann et al., 2008). Hsp26p belongs to a specialized class of proteins known as long-lived asymmetrically retained proteins (LARP), which have the ability to form distinct cytoplasmic foci that can be visualized microscopically. These Hsp26p-containing foci emerge when cells enter the stationary phase or following exposure to heat stress. Notably, these localized clusters, which may be directly associated with protein aggregates, are retained almost exclusively within the mother cells upon re-entry into the proliferative state or following recovery to normal physiological temperatures (Thayer et al., 2014).

This intricate system of protein quality control highlights the essential role of molecular chaperones in cellular homeostasis and demonstrates how asymmetric inheritance of damaged or aggregated proteins serves as a crucial mechanism for maintaining the viability and longevity of progeny cells.

The restriction of protein aggregates by an aging mother cell is a complex and tightly regulated process that necessitates the involvement of genes responsible for generating cellular asymmetry (AGG). These genes orchestrate the uneven inheritance of aggregated proteins, ensuring that damaged or misfolded proteins are retained in the mother cell while daughter cells

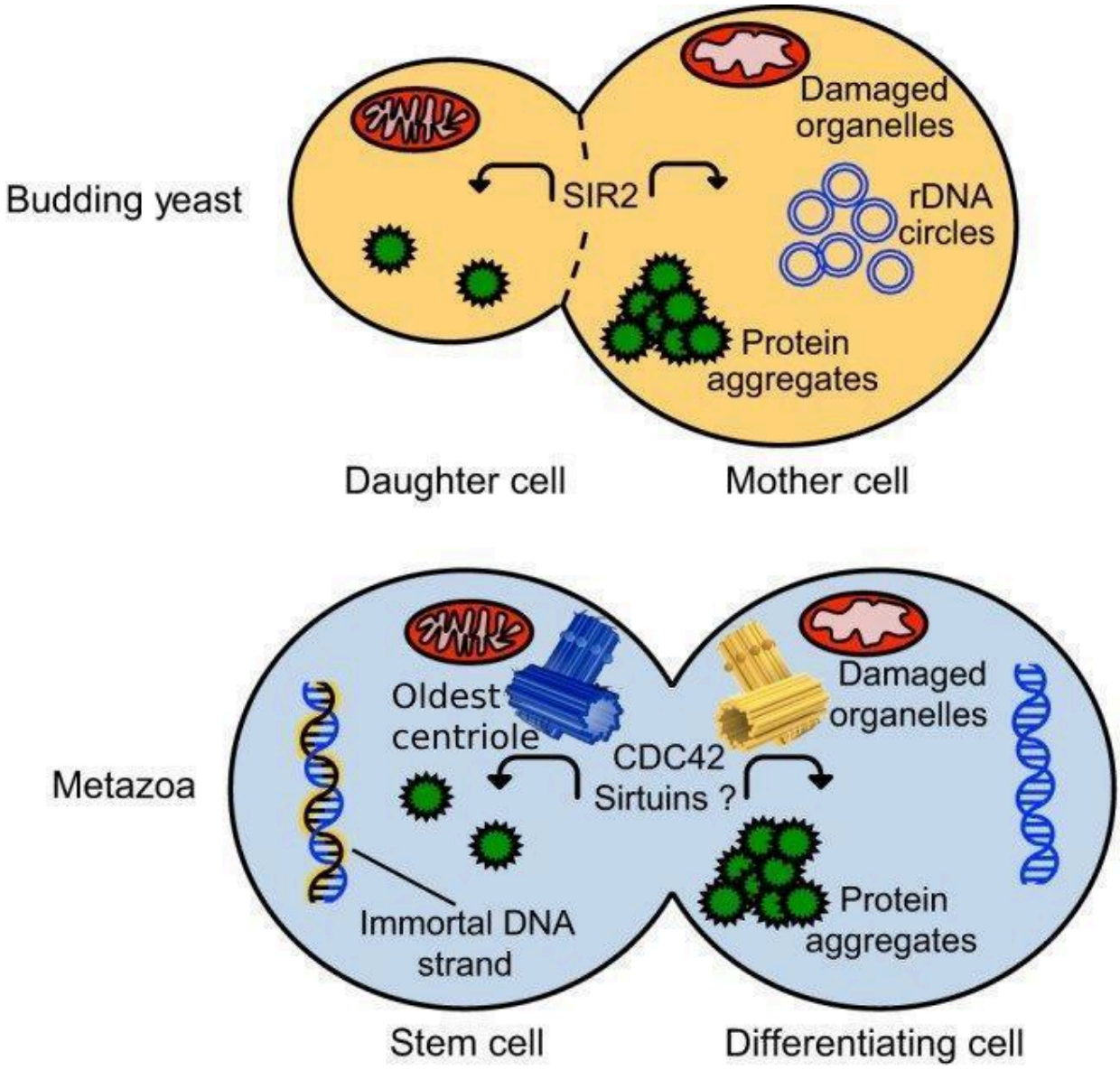
inherit a proteome of higher quality. A recent genome-wide screening for AGG candidates in yeast has highlighted the role of vesicular trafficking, membrane fusion, and myosin-dependent vacuole inheritance in this asymmetric process.

For instance, it has been demonstrated that the vacuole inheritance adapter protein Vac17 and the endocytic vesicle-associated dynamin-like protein Vps1 regulate asymmetry and replicative lifespan through Myo2-dependent effects on endocytosis and spatial protein quality control (Hill et al., 2016). Furthermore, asymmetric segregation of protein aggregates in yeast may also be facilitated through compartmentalization of the endoplasmic reticulum (ER). Specifically, protein deposit precursors, which consist of misfolded proteins and aggregation seeds, are captured by the ER membrane-associated chaperone Ydj1. Subsequently, an ER lateral diffusion barrier—a specialized ER membrane domain located at the bud neck that demarcates the maternal ER from that of the bud (Clay et al., 2014)—further promotes asymmetric partitioning of aggregates (Saarikangas et al., 2017).

The asymmetric segregation of damaged proteins is not confined to yeast but is involved in various crucial biological processes, including neuroprotection in multicellular organisms and the rejuvenation of newborn microbial cells either during successive divisions or in response to environmental stress recovery (Moore and Jessberger, 2017). Notably, ER diffusion barriers have also been shown to facilitate the asymmetric segregation of damaged proteins between the daughter cells of mammalian neural stem cells (Moore et al., 2015).

Mitochondria, the powerhouses of the cell, are essential for ATP production and cellular energy metabolism. Their precise segregation is crucial for maintaining cellular health and ensuring the proper fate of sibling cells (Mishra and Chan, 2014). In yeast, the distribution of mitochondria to the buds is tightly regulated, whereas the amount of mitochondria retained in the mother cell progressively declines with age (Rafelski et al., 2012). It is hypothesized that older, less functional mitochondria are preferentially retained in the mother cell, while buds receive highly functional organelles (Pernice et al., 2016). The anterograde (bud-directed) transport of mitochondria is mediated by Myo2 (Chernyakov et al., 2013). A recent genetic screen has uncovered an unexpected interaction between myo2 and genes required for mitochondrial fusion; when Myo2 transport capacity is constrained, mitochondria must be in a fused state to ensure an adequate mitochondrial supply to the bud. Conversely, fused mitochondria support the retention of a critical mitochondrial population in the mother cell when bud-directed transport is enhanced (Böckler et al., 2017). Intriguingly, mechanisms that govern the sequestration of damaged cytosolic proteins and aggregates in the mother cell may also contribute to biased mitochondrial inheritance (Zhou et al., 2014). Based on these findings, it has been proposed that minimal Myo2 activity is required for mitochondrial retention in the mother cell and for aggregate capture, thereby securing aggregate sequestration. In contrast, heightened Myo2 activity promotes the transport of mitochondria-associated aggregates to the bud, disrupting aggregate retention. Thus, finely tuned Myo2-dependent mitochondrial transport is essential for confining cytosolic protein aggregates within the mother cell.

Figure 1. Selective inheritance of newly formed structures and organelles during the transfer of the old maternal centriole to the sibling that maintains stem-like potential



Evidence linking asymmetric mitochondrial inheritance to stemness has also emerged. Human mammary epithelial stem-like cells (SLCs) inherit fewer old mitochondria and maintain stem cell properties, as reflected in their capacity to form mammospheres (Katajisto et al., 2015). Stem cells often sequester mitochondria containing aged proteins into distinct subcellular domains through a mechanism involving the dynamin-related protein Drp1, a key mediator of mitochondrial fission and autophagy (Mao et al., 2013). Disrupting mitochondrial fission impairs both age-associated subcellular localization and mitochondrial segregation, leading to the loss of stemness in daughter cells. Notably, SLCs exhibit an elevated mitophagy-to-autophagy ratio, suggesting that mitochondrial quality is critical for SLC identity and for asymmetric mitochondrial inheritance. This implies that any perturbation compromising mitochondrial quality control

mechanisms would either act as a signal prompting SLCs to halt asymmetric mitochondrial segregation or, alternatively, overwhelm their ability to efficiently partition aged mitochondria. Remarkably, the stem cell sibling that retains the parental stem-like potential selectively inherits all newly synthesized molecules, structures, and organelles—yet, at the same time, it exclusively inherits the old maternal centriole.

A Drp1-dependent mechanism has also been observed in activated lymphocytes, which utilize asymmetric cell division (ACD) to coordinate differentiation and self-renewal (Adams et al., 2016). Here, uneven elimination of aged mitochondria dictates differential sibling cell fates: daughter cells that purge more mitochondria undergo self-renewal, whereas sibling cells that retain more mitochondria proceed toward differentiation. Correspondingly, genetic and pharmacological inhibition of Drp1 enhances differentiation and elevates mitochondrial and cellular reactive oxygen species (ROS) levels. Cells exhibiting higher mitochondrial ROS accumulation exhibit impaired clearance of aged mitochondria. Conversely, ROS scavenging via N-acetyl-L-cysteine (NAC) enhances mitochondrial clearance and promotes self-renewal. Confocal microscopy has revealed that the subcellular distribution of aged mitochondria is largely symmetrical during metaphase and early telophase. However, as cytokinesis progresses, mitochondrial abundance frequently becomes skewed between sibling cells. In summary, ROS signaling plays a pivotal role in facilitating the removal of aged mitochondria in differentiated daughter cells.

Mitochondrial asymmetry is also evident during meiosis I in mice, where the majority of mitochondria are retained in the oocyte rather than the polar body, which ultimately degenerates (Dalton and Carroll, 2013). This asymmetric mitochondrial distribution is crucial, as oocytes do not replicate mitochondria until fertilization. Moreover, blocking glycolysis before the blastocyst stage renders mitochondria the sole ATP source during early embryonic development (Dumollard et al., 2007). Biased mitochondrial partitioning during meiosis involves meiotic spindle mechanisms and spindle displacement. Initially, mitochondria accumulate around the spindle but are then transported toward the oocyte side along microtubules in a kinesin- and dynein-dependent manner. Subsequently, the meiotic spindle migrates toward the cortex during polar body extrusion in meiosis I (Ledan et al., 2001). This spindle migration process necessitates the actin cytoskeleton; in its absence, mitochondria remain symmetrically distributed (Mogessie et al., 2018).

Similarly, lysosomes segregate asymmetrically in dividing keratinocytes, concentrating near the centrosomal side of the nucleus just before mitosis and subsequently partitioning preferentially into one daughter cell (Lång et al., 2018). Keratinocytes enriched with lysosomes exhibit higher colony turnover rates, a hallmark of human keratinocyte stemness (Nanba et al., 2016), and give rise to colonies expressing the stem cell marker cytokeratin 15 (K15; KRT15).

Hematopoietic stem cells (HSCs) also exhibit biased segregation of the cellular degradation machinery, including lysosomes, autophagosomes, and mitophagosomes, during asymmetric divisions (Loeffler et al., 2019). Furthermore, asymmetric segregation of Numb, a Notch

signaling inhibitor (Kovall et al., 2017), has been reported in HSCs, influencing metabolic activation and differentiation potential in daughter cells.

Since the initial description of asymmetric cell division (ACD) in 1905, significant progress has been made in uncovering the molecular and cellular mechanisms underlying this process. However, numerous fundamental questions remain unresolved, particularly regarding the role of size asymmetry between daughter cells in determining cell fate decisions and the precise mechanisms through which this occurs. Furthermore, the contribution of both intrinsic and extrinsic mechanical forces to cell polarization and the biased segregation of macromolecules is an area that remains largely unexplored. Of particular interest is the paradox of the inheritance of the oldest centriole by the daughter cell that retains the stemness potential of the parental cell—a phenomenon that demands further detailed investigation.

Is Irreversible Differentiation Regulated by an Intrinsic Signal or an Extrinsic Factor?

Waddington's epigenetic landscape remains one of the most profound conceptual frameworks for understanding cell lineage determination and the differentiation of progeny cells (Waddington CH, 1957). Over the past several decades, this insightful metaphor has guided researchers in formulating diverse models of cell fate decision-making (MacArthur, 2023). By integrating various quantitative models and analyzing the multitude of factors that influence fate determination, scientists have progressively refined and expanded upon Waddington's landscape (Shakiba et al., 2022). Nevertheless, a critical unresolved question remains: is the landscape static and predetermined, or is it dynamically influenced by intrinsic noise or extrinsic signaling factors (Stanoev, A., & Koseska, A., 2022)?

On one hand, some researchers argue that cells exist within a stationary epigenetic landscape, where fate decisions occur via discrete transitions between distinct valleys (Desai et al., 2021), driven by a phenomenon known as "regulated noise" in gene expression (Guillemin, A., & Stumpf, M. P. H., 2021). This perspective suggests that stochastic fluctuations in gene expression play a dominant role in cell fate commitment. Conversely, other studies support the idea that the epigenetic landscape is not fixed but dynamically reshaped during cell fate transitions. In this model, modifications to the landscape itself orchestrate fate changes (Hota et al., 2022) and are primarily controlled by external signaling inputs.

Within the framework of noise-driven regulation, shifts in cell fate decisions are largely dictated by the spontaneous heterogeneity of gene expression within a given cell population (Wheat et al., 2020). Consequently, the initial cellular state significantly influences the trajectory of fate determination. For instance, Chang et al. (Chang et al., 2008) demonstrated that hematopoietic stem cells (HSCs) exhibit an inherent and stable heterogeneity in the expression levels of Scal-1, also known as Ly-6 (Van De Rijn et al., 1989). Notably, discrete populations characterized by different levels of Scal-1 expression display distinct predispositions toward specific lineage commitments.

In contrast, within the framework of signal-driven regulation, cell fate is dictated primarily by extrinsic factors, including cytokines, chemical cues, mechanical forces, and genetic regulatory elements, all of which dynamically remodel the epigenetic landscape. In this case, the influence of the initial cellular state on fate decisions is relatively negligible. Given the ability to modulate signaling pathways experimentally, the signal-driven model has been extensively utilized in cell fate engineering (Del Vecchio et al., 2017). This has led to the development of in vitro induction systems centered around the generation of induced pluripotent stem cells (iPSCs) for the production of specific, desired cell types (Ng et al., 2021). Collectively, these driving forces provide a foundational framework for decoding the mechanisms governing fate decisions and understanding key aspects of organismal development (Simon et al., 2018). By dissecting the interplay between noise-driven and signal-driven regulatory mechanisms, researchers can refine their understanding of cell differentiation processes in vivo, oncogenic transformation, and the reprogramming potential of cells in vitro.

Nevertheless, the fundamental forces that govern the fate decisions of daughter cells during asymmetric division and differentiation remain elusive. The centriole-based differentiation theory proposes a direct link between differentiation inducers and centrioles—suggesting that irreversible differentiation is not primarily governed by nuclear cues but rather by cytoplasmic, intracellular signaling mechanisms that dictate fate commitment. Further investigation is required to elucidate the precise mechanisms by which centrioles influence these critical processes.

References:

1. Abeysundara, N., Simmonds, A. J., & Hughes, S. C. (2018). Moesin is involved in polarity maintenance and cortical remodeling during asymmetric cell division. Molecular Biology of the Cell, 29(4), 419-434.
2. Adams, W. C., Chen, Y. H., Kratchmarov, R., Yen, B., Nish, S. A., Lin, W. H. W., ... & Reiner, S. L. (2016). Anabolism-associated mitochondrial stasis driving lymphocyte differentiation over self-renewal. Cell reports, 17(12), 3142-3152.
3. Akera, T., Chmátal, L., Trimm, E., Yang, K., Aonbangkhen, C., Chenoweth, D. M., ... & Lampson, M. A. (2017). Spindle asymmetry drives non-Mendelian chromosome segregation. Science, 358(6363), 668-672.
4. Akera, T., Trimm, E., & Lampson, M. A. (2019). Molecular strategies of meiotic cheating by selfish centromeres. Cell, 178(5), 1132-1144.
5. Alliegro, M. C., Alliegro, M. A., & Palazzo, R. E. (2006). Centrosome-associated RNA in surf clam oocytes. Proceedings of the National Academy of Sciences, 103(24), 9034-9038.
6. Allshire, R. C., & Karpen, G. H. (2008). Epigenetic regulation of centromeric chromatin: old dogs, new tricks?. Nature Reviews Genetics, 9(12), 923-937.
7. Atwood, S. X., & Prehoda, K. E. (2009). aPKC phosphorylates Miranda to polarize fate determinants during neuroblast asymmetric cell division. Current Biology, 19(9), 723-729.
8. Babour, A., Bicknell, A. A., Tourtellotte, J., & Niwa, M. (2010). A surveillance pathway monitors the fitness of the endoplasmic reticulum to control its inheritance. Cell, 142(2), 256-269.
9. Bärenz, F., Kschonsak, Y. T., Meyer, A., Jafarpour, A., Lorenz, H., & Hoffmann, I. (2018). Ccdc61 controls centrosomal localization of Cep170 and is required for spindle assembly and symmetry. Molecular biology of the cell, 29(26), 3105-3118.
10. Barros, C. S., Phelps, C. B., & Brand, A. H. (2003). Drosophila nonmuscle myosin II promotes the asymmetric segregation of cell fate determinants by cortical exclusion rather than active transport. Developmental cell, 5(6), 829-840.
11. Beaudouin, J., Gerlich, D., Daigle, N., Eils, R., & Ellenberg, J. (2002). Nuclear envelope breakdown proceeds by microtubule-induced tearing of the lamina. Cell, 108(1), 83-96.

12. Böckler, S., Chelius, X., Hock, N., Klecker, T., Wolter, M., Weiss, M., ... & Westermann, B. (2017). Fusion, fission, and transport control asymmetric inheritance of mitochondria and protein aggregates. Journal of Cell Biology, 216(8), 2481-2498.
13. Bouvrette, L. P. B., Cody, N. A., Bergalet, J., Lefebvre, F. A., Diot, C., Wang, X., ... & Lécuyer, E. (2018). CeFra-seq reveals broad asymmetric mRNA and noncoding RNA distribution profiles in Drosophila and human cells. Rna, 24(1), 98-113.
14. Boxem, M., & van den Heuvel, S. (2019). Cell polarity: getting the PARty started. Current Biology, 29(13), R637-R639.
15. Cabernard, C., Prehoda, K. E., & Doe, C. Q. (2010). A spindle-independent cleavage furrow positioning pathway. Nature, 467(7311), 91-94.
16. Cai, Y., Yu, F., Lin, S., Chia, W., & Yang, X. (2003). Apical complex genes control mitotic spindle geometry and relative size of daughter cells in Drosophila neuroblast and pI asymmetric divisions. Cell, 112(1), 51-62.
17. Cashikar, A. G., Duennwald, M., & Lindquist, S. L. (2005). A chaperone pathway in protein disaggregation: Hsp26 alters the nature of protein aggregates to facilitate reactivation by Hsp104. Journal of Biological Chemistry, 280(25), 23869-23875.
18. Chang, H. H., Hemberg, M., Barahona, M., Ingber, D. E., & Huang, S. (2008). Transcriptome-wide noise controls lineage choice in mammalian progenitor cells. Nature, 453(7194), 544–547. https://doi.org/10.1038/nature06965
19. Chen, C., Inaba, M., Venkei, Z. G., & Yamashita, Y. M. (2016). Klp10A, a stem cell centrosome-enriched kinesin, balances asymmetries in Drosophila male germline stem cell division. Elife, 5, e20977.
20. Chen, J. Y., Bottjer, D. J., Davidson, E. H., Dornbos, S. Q., Gao, X., Yang, Y. H., ... & Tafforeau, P. (2006). Phosphatized polar lobe-forming embryos from the Precambrian of southwest China. Science, 312(5780), 1644-1646.
21. Chen, X., Widmer, L. A., Stangier, M. M., Steinmetz, M. O., Stelling, J., & Barral, Y. (2019). Remote control of microtubule plus-end dynamics and function from the minus-end. Elife, 8, e48627.
22. Chernyakov, I., Santiago-Tirado, F., & Bretscher, A. (2013). Active segregation of yeast mitochondria by Myo2 is essential and mediated by Mmr1 and Ypt11. Current Biology, 23(18), 1818-1824.
23. Chichinadze, K. N., & Tkemaladze, D. V. (2008). Centrosomal hypothesis of cellular aging and differentiation. Advances in Gerontology= Uspekhi Gerontologii, 21(3), 367-371.
24. Chichinadze, K., Lazarashvili, A., & Tkemaladze, J. (2013). RNA in centrosomes: structure and possible functions. Protoplasma, 250(1), 397-405.
25. Chichinadze, K., Tkemaladze, D., & Lazarashvili, A. (2012). New class of RNA and centrosomal hypothesis of cell aging. Advances in Gerontology= Uspekhi Gerontologii, 25(1), 23-28.
26. Chichinadze, K., Tkemaladze, J., & Lazarashvili, A. (2012). A new class of RNAs and the centrosomal hypothesis of cell aging. Advances in Gerontology, 2(4), 287-291.
27. Chichinadze, K., Tkemaladze, J., & Lazarashvili, A. (2012). Discovery of centrosomal RNA and centrosomal hypothesis of cellular ageing and differentiation. Nucleosides, Nucleotides and Nucleic Acids, 31(3), 172-183.
28. Choksi, S. P., Southall, T. D., Bossing, T., Edoff, K., de Wit, E., Fischer, B. E., ... & Brand, A. H. (2006). Prospero acts as a binary switch between self-renewal and differentiation in Drosophila neural stem cells. Developmental cell, 11(6), 775-789.
29. Clay, L., Caudron, F., Denoth-Lippuner, A., Boettcher, B., Buvelot Frei, S., Snapp, E. L., & Barral, Y. (2014). A sphingolipid-dependent diffusion barrier confines ER stress to the yeast mother cell. Elife, 3, e01883.
30. Conduit, P. T., & Raff, J. W. (2010). Cnn dynamics drive centrosome size asymmetry to ensure daughter centriole retention in Drosophila neuroblasts. Current Biology, 20(24), 2187-2192.
31. Conduit, P. T., Wainman, A., & Raff, J. W. (2015). Centrosome function and assembly in animal cells. Nature reviews Molecular cell biology, 16(10), 611-624.
32. Conklin, E. G. (1905). Mosaic development in ascidian eggs. Journal of Experimental Zoology, 2(2), 145-223.
33. Connell, M., Cabernard, C., Ricketson, D., Doe, C. Q., & Prehoda, K. E. (2011). Asymmetric cortical extension shifts cleavage furrow position in Drosophila neuroblasts. Molecular biology of the cell, 22(22), 4220-4226.
34. Coumailleau, F., Fürthauer, M., Knoblich, J. A., & Gonzalez-Gaitan, M. (2009). Directional Delta and Notch trafficking in Sara endosomes during asymmetric cell division. Nature, 458(7241), 1051-1055.

35. Dalton, C. M., & Carroll, J. (2013). Biased inheritance of mitochondria during asymmetric cell division in the mouse oocyte. Journal of cell science, 126(13), 2955-2964.
36. Del Arco, A. G., Edgar, B. A., & Erhardt, S. (2018). In vivo analysis of centromeric proteins reveals a stem cell-specific asymmetry and an essential role in differentiated, non-proliferating cells. Cell reports, 22(8), 1982-1993.
37. Del Vecchio, D., Abdallah, H., Qian, Y., & Collins, J. J. (2017). A Blueprint for a Synthetic Genetic Feedback Controller to Reprogram Cell Fate. Cell systems, 4(1), 109–120.e11. https://doi.org/10.1016/j.cels.2016.12.001
38. Derivery, E., Seum, C., Daeden, A., Loubéry, S., Holtzer, L., Jülicher, F., & Gonzalez-Gaitan, M. (2015). Polarized endosome dynamics by spindle asymmetry during asymmetric cell division. Nature, 528(7581), 280-285.
39. Desai, R. V., Chen, X., Martin, B., Chaturvedi, S., Hwang, D. W., Li, W., Yu, C., Ding, S., Thomson, M., Singer, R. H., Coleman, R. A., Hansen, M. M. K., & Weinberger, L. S. (2021). A DNA repair pathway can regulate transcriptional noise to promote cell fate transitions. Science (New York, N.Y.), 373(6557), eabc6506. https://doi.org/10.1126/science.abc6506
40. Dumollard, R., Duchen, M., & Carroll, J. (2007). Current topics in developmental biology. Curr. Top. Dev. Biol., 77, 21-49.
41. Feng, Z., Caballe, A., Wainman, A., Johnson, S., Haensele, A. F., Cottee, M. A., ... & Raff, J. W. (2017). Structural basis for mitotic centrosome assembly in flies. Cell, 169(6), 1078-1089.
42. Franzmann, T. M., Menhorn, P., Walter, S., & Buchner, J. (2008). Activation of the chaperone Hsp26 is controlled by the rearrangement of its thermosensor domain. Molecular cell, 29(2), 207-216.
43. Fusco, D., Accornero, N., Lavoie, B., Shenoy, S. M., Blanchard, J. M., Singer, R. H., & Bertrand, E. (2003). Single mRNA molecules demonstrate probabilistic movement in living mammalian cells. Current Biology, 13(2), 161-167.
44. Gallaud, E., Pham, T., & Cabernard, C. (2017). Drosophila melanogaster neuroblasts: a model for asymmetric stem cell divisions. Asymmetric Cell Division in Development, Differentiation and Cancer, 183-210.
45. Gambarotto, D., Pennetier, C., Ryniawec, J. M., Buster, D. W., Gogendeau, D., Goupil, A., ... & Basto, R. (2019). Plk4 regulates centriole asymmetry and spindle orientation in neural stem cells. Developmental cell, 50(1), 11-24.
46. Guillemin, A., & Stumpf, M. P. H. (2021). Noise and the molecular processes underlying cell fate decision-making. Physical biology, 18(1), 011002. https://doi.org/10.1088/1478-3975/abc9d1
47. Hannaford, M. R., Ramat, A., Loyer, N., & Januschke, J. (2018). aPKC-mediated displacement and actomyosin-mediated retention polarize Miranda in Drosophila neuroblasts. Elife, 7, e29939.
48. Hejnol, A., & Pfannenstiel, H. D. (1998). Myosin and actin are necessary for polar lobe formation and resorption in Ilyanassa obsoleta embryos. Development genes and evolution, 208, 229-233.
49. Hibbel, A., Bogdanova, A., Mahamdeh, M., Jannasch, A., Storch, M., Schäffer, E., ... & Howard, J. (2015). Kinesin Kip2 enhances microtubule growth in vitro through length-dependent feedback on polymerization and catastrophe. Elife, 4, e10542.
50. Hill, S. M., Hao, X., Grönvall, J., Spikings-Nordby, S., Widlund, P. O., Amen, T., ... & Nyström, T. (2016). Asymmetric inheritance of aggregated proteins and age reset in yeast are regulated by Vac17-dependent vacuolar functions. Cell reports, 16(3), 826-838.
51. Holly, R. W., Jones, K., & Prehoda, K. E. (2020). A conserved PDZ-binding motif in aPKC interacts with Par-3 and mediates cortical polarity. Current Biology, 30(5), 893-898.
52. Hota, S. K., Rao, K. S., Blair, A. P., Khalilimeybodi, A., Hu, K. M., Thomas, R., So, K., Kameswaran, V., Xu, J., Polacco, B. J., Desai, R. V., Chatterjee, N., Hsu, A., Muncie, J. M., Blotnick, A. M., Winchester, S. A. B., Weinberger, L. S., Hüttenhain, R., Kathiriya, I. S., Krogan, N. J., … Bruneau, B. G. (2022). Brahma safeguards canalization of cardiac mesoderm differentiation. Nature, 602(7895), 129–134. https://doi.org/10.1038/s41586-021-04336-y
53. Jaba, T. (2022). Dasatinib and quercetin: short-term simultaneous administration yields senolytic effect in humans. Issues and Developments in Medicine and Medical Research Vol. 2, 22-31.
54. Jakobsen, L., Vanselow, K., Skogs, M., Toyoda, Y., Lundberg, E., Poser, I., ... & Andersen, J. S. (2011). Novel asymmetrically localizing components of human centrosomes identified by complementary proteomics methods. The EMBO journal, 30(8), 1520-1535.

55. Januschke, J., Llamazares, S., Reina, J., & Gonzalez, C. (2011). Drosophila neuroblasts retain the daughter centrosome. Nature communications, 2(1), 243.
56. Jeffery, W. R., Tomlinson, C. R., & Brodeur, R. D. (1983). Localization of actin messenger RNA during early ascidian development. Developmental biology, 99(2), 408-417.
57. Jonas, F. R., Royle, K. E., Aw, R., Stan, G. B. V., & Polizzi, K. M. (2018). Investigating the consequences of asymmetric endoplasmic reticulum inheritance in Saccharomyces cerevisiae under stress using a combination of single cell measurements and mathematical modelling. Synthetic and Systems Biotechnology, 3(1), 64-75.
58. Juliano, C. E., Voronina, E., Stack, C., Aldrich, M., Cameron, A. R., & Wessel, G. M. (2006). Germ line determinants are not localized early in sea urchin development, but do accumulate in the small micromere lineage. Developmental biology, 300(1), 406-415.
59. Katajisto, P., Döhla, J., Chaffer, C. L., Pentinmikko, N., Marjanovic, N., Iqbal, S., ... & Sabatini, D. M. (2015). Asymmetric apportioning of aged mitochondria between daughter cells is required for stemness. Science, 348(6232), 340-343.
60. Kemphues, K. J., Priess, J. R., Morton, D. G., & Cheng, N. (1988). Identification of genes required for cytoplasmic localization in early C. elegans embryos. Cell, 52(3), 311-320.
61. Kingsley, E. P., Chan, X. Y., Duan, Y., & Lambert, J. D. (2007). Widespread RNA segregation in a spiralian embryo. Evolution & development, 9(6), 527-539.
62. Kipshidze, M., & Tkemaladze, J. (2023). Comparative Analysis of drugs that improve the Quality of Life and Life Expectancy. Junior Researchers, 1(1), 184–193. doi: https://doi.org/10.52340/2023.01.01.19
63. Kipshidze, M., & Tkemaladze, J. (2023). The planaria Schmidtea mediterranea as a model system for the study of stem cell biology. Junior Researchers, 1(1), 194–218. doi: https://doi.org/10.52340/2023.01.01.20
64. Kipshidze, M., & Tkemaladze, J. (2024). Abastumani Resort: Balneological Heritage and Modern Potential. Junior Researchers, 2(2), 126–134. doi: https://doi.org/10.52340/jr.2024.02.02.12
65. Kipshidze, M., & Tkemaladze, J. (2024). Balneology in Georgia: traditions and modern situation. Junior Researchers, 2(2), 78–97. doi: https://doi.org/10.52340/jr.2024.02.02.09
66. Kipshidze, M., & Tkemaladze, J. (2024). Microelementoses - history and current status. Junior Researchers, 2(2), 108–125. doi: https://doi.org/10.52340/jr.2024.02.02.11
67. Kiyomitsu, T. (2019). The cortical force-generating machinery: how cortical spindle-pulling forces are generated. Current opinion in cell biology, 60, 1-8.'
68. Klinkert, K., Levernier, N., Gross, P., Gentili, C., von Tobel, L., Pierron, M., ... & Gönczy, P. (2019). Aurora A depletion reveals centrosome-independent polarization mechanism in Caenorhabditis elegans. Elife, 8, e44552.
69. Kovall, R. A., Gebelein, B., Sprinzak, D., & Kopan, R. (2017). The canonical Notch signaling pathway: structural and biochemical insights into shape, sugar, and force. Developmental cell, 41(3), 228-241.
70. Kursel, L. E., & Malik, H. S. (2018). The cellular mechanisms and consequences of centromere drive. Current Opinion in Cell Biology, 52, 58-65.
71. Kusek, G., Campbell, M., Doyle, F., Tenenbaum, S. A., Kiebler, M., & Temple, S. (2012). Asymmetric segregation of the double-stranded RNA binding protein Staufen2 during mammalian neural stem cell divisions promotes lineage progression. Cell stem cell, 11(4), 505-516.
72. Lambert, J. D., & Nagy, L. M. (2002). Asymmetric inheritance of centrosomally localized mRNAs during embryonic cleavages. Nature, 420(6916), 682-686.
73. Landskron, L., Steinmann, V., Bonnay, F., Burkard, T. R., Steinmann, J., Reichardt, I., ... & Knoblich, J. A. (2018). The asymmetrically segregating lncRNA cherub is required for transforming stem cells into malignant cells. Elife, 7, e31347.
74. Lécuyer, E., Yoshida, H., Parthasarathy, N., Alm, C., Babak, T., Cerovina, T., ... & Krause, H. M. (2007). Global analysis of mRNA localization reveals a prominent role in organizing cellular architecture and function. Cell, 131(1), 174-187.
75. Ledan, E., Polanski, Z., Terret, M. E., & Maro, B. (2001). Meiotic maturation of the mouse oocyte requires an equilibrium between cyclin B synthesis and degradation. Developmental biology, 232(2), 400-413.
76. Lengefeld, J., Yen, E., Chen, X., Leary, A., Vogel, J., & Barral, Y. (2018). Spatial cues and not spindle pole maturation drive the asymmetry of astral microtubules between new and preexisting spindle poles. Molecular biology of the cell, 29(1), 10-28.

77. Lerit, D. A., & Rusan, N. M. (2013). PLP inhibits the activity of interphase centrosomes to ensure their proper segregation in stem cells. Journal of Cell Biology, 202(7), 1013-1022.
78. Lezhava, T., Monaselidze, J., Jokhadze, T., Kakauridze, N., Khodeli, N., Rogava, M., Tkemaladze, J., ... & Gaiozishvili, M. (2011). Gerontology research in Georgia. Biogerontology, 12, 87-91. doi: 10.1007/s10522-010-9283-6. Epub 2010 May 18. PMID: 20480236; PMCID: PMC3063552
79. Li, P., Yang, X., Wasser, M., Cai, Y., & Chia, W. (1997). Inscuteable and Staufen Mediate Asymmetric Localization and Segregation of prosperoRNA during Drosophila Neuroblast Cell Divisions. Cell, 90(3), 437-447.
80. Liberek, K., Lewandowska, A., & Ziętkiewicz, S. (2008). Chaperones in control of protein disaggregation. The EMBO journal, 27(2), 328-335.
81. Loeffler, D., Wehling, A., Schneiter, F., Zhang, Y., Müller-Bötticher, N., Hoppe, P. S., ... & Schroeder, T. (2019). Asymmetric lysosome inheritance predicts activation of haematopoietic stem cells. Nature, 573(7774), 426-429.
82. Long, R. M., Singer, R. H., Meng, X., Gonzalez, I., Nasmyth, K., & Jansen, R. P. (1997). Mating type switching in yeast controlled by asymmetric localization of ASH1 mRNA. Science, 277(5324), 383-387.
83. Loyer, N., & Januschke, J. (2020). Where does asymmetry come from? Illustrating principles of polarity and asymmetry establishment in Drosophila neuroblasts. Current Opinion in Cell Biology, 62, 70-77.
84. MacArthur B. D. (2023). Stem cell biology needs a theory. Stem cell reports, 18(1), 3–5. https://doi.org/10.1016/j.stemcr.2022.11.005
85. Manzano-López, J., Matellán, L., Álvarez-Llamas, A., Blanco-Mira, J. C., & Monje-Casas, F. (2019). Asymmetric inheritance of spindle microtubule-organizing centres preserves replicative lifespan. Nature Cell Biology, 21(8), 952-965.
86. Mao, K., Wang, K., Liu, X., & Klionsky, D. J. (2013). The scaffold protein Atg11 recruits fission machinery to drive selective mitochondria degradation by autophagy. Developmental cell, 26(1), 9-18.
87. Matsaberidze, M., Prangishvili, A., Gasitashvili, Z., Chichinadze, K., & Tkemaladze, J. (2017). TO TOPOLOGY OF ANTI-TERRORIST AND ANTI-CRIMINAL TECHNOLOGY FOR EDUCATIONAL PROGRAMS. International Journal of Terrorism & Political Hot Spots, 12.
88. Matsuzaki, F., Ohshiro, T., Ikeshima-Kataoka, H., & Izumi, H. (1998). Miranda localizes staufen and prospero asymmetrically in mitotic neuroblasts and epithelial cells in early Drosophila embryogenesis. Development, 125(20), 4089-4098.
89. Mishra, P., & Chan, D. C. (2014). Mitochondrial dynamics and inheritance during cell division, development and disease. Nature reviews Molecular cell biology, 15(10), 634-646.
90. Mogessie, B., Scheffler, K., & Schuh, M. (2018). Assembly and positioning of the oocyte meiotic spindle. Annual review of cell and developmental biology, 34(1), 381-403.
91. Mogessie, B., Scheffler, K., & Schuh, M. (2018). Assembly and positioning of the oocyte meiotic spindle. Annual review of cell and developmental biology, 34(1), 381-403.
92. Mollinari, C., Lange, B., & González, C. (2002). Miranda, a protein involved in neuroblast asymmetric division, is associated with embryonic centrosomes of Drosophila melanogaster. Biology of the Cell, 94(1), 1-13.
93. Moore, D. L., & Jessberger, S. (2017). Creating age asymmetry: consequences of inheriting damaged goods in mammalian cells. Trends in cell biology, 27(1), 82-92.
94. Moore, D. L., Pilz, G. A., Araúzo-Bravo, M. J., Barral, Y., & Jessberger, S. (2015). A mechanism for the segregation of age in mammalian neural stem cells. Science, 349(6254), 1334-1338.
95. Morgan, T. H. (1933). The formation of the antipolar lobe in Ilyanassa. Journal of Experimental Zoology, 64(3), 433-467.
96. Munro, E., Nance, J., & Priess, J. R. (2004). Cortical flows powered by asymmetrical contraction transport PAR proteins to establish and maintain anterior-posterior polarity in the early C. elegans embryo. Developmental cell, 7(3), 413-424.
97. Nair, A. R., Singh, P., Garcia, D. S., Rodriguez-Crespo, D., Egger, B., & Cabernard, C. (2016). The microcephaly-associated protein Wdr62/CG7337 is required to maintain centrosome asymmetry in Drosophila neuroblasts. Cell reports, 14(5), 1100-1113.
98. Nanba, D., Toki, F., Tate, S., Imai, M., Matsushita, N., Toki, H., ... & Barrandon, Y. (2016). Cell motion predicts human epidermal stemness. Journal of Dermatological Science, 84(1), e51.

99. Ng, A. H. M., Khoshakhlagh, P., Rojo Arias, J. E., Pasquini, G., Wang, K., Swiersy, A., Shipman, S. L., Appleton, E., Kiaee, K., Kohman, R. E., Vernet, A., Dysart, M., Leeper, K., Saylor, W., Huang, J. Y., Graveline, A., Taipale, J., Hill, D. E., Vidal, M., Melero-Martin, J. M., … Church, G. M. (2021). A comprehensive library of human transcription factors for cell fate engineering. Nature biotechnology, 39(4), 510–519. https://doi.org/10.1038/s41587-020-0742-6
100. Oon, C. H., & Prehoda, K. E. (2019). Asymmetric recruitment and actin-dependent cortical flows drive the neuroblast polarity cycle. Elife, 8, e45815.
101. Ou, G., Stuurman, N., D'Ambrosio, M., & Vale, R. D. (2010). Polarized myosin produces unequal-size daughters during asymmetric cell division. Science, 330(6004), 677-680.
102. Pereira, G., Tanaka, T. U., Nasmyth, K., & Schiebel, E. (2001). Modes of spindle pole body inheritance and segregation of the Bfa1p–Bub2p checkpoint protein complex. The EMBO journal, 20(22), 6359-6370.
103. Pernice, W. M., Vevea, J. D., & Pon, L. A. (2016). A role for Mfb1p in region-specific anchorage of high-functioning mitochondria and lifespan in Saccharomyces cerevisiae. Nature communications, 7(1), 10595.
104. Pham, T. T., Monnard, A., Helenius, J., Lund, E., Lee, N., Müller, D. J., & Cabernard, C. (2019). Spatiotemporally controlled myosin relocalization and internal pressure generate sibling cell size asymmetry. Iscience, 13, 9-19.
105. Piña, F. J., & Niwa, M. (2015). The ER Stress Surveillance (ERSU) pathway regulates daughter cell ER protein aggregate inheritance. Elife, 4, e06970.
106. Poon, J., Fries, A., Wessel, G. M., & Yajima, M. (2019). Evolutionary modification of AGS protein contributes to formation of micromeres in sea urchins. Nature Communications, 10(1), 3779.
107. Prangishvili, A., Gasitashvili, Z., Matsaberidze, M., Chkhartishvili, L., Chichinadze, K., Tkemaladze, J., ... & Azmaiparashvili, Z. (2019). SYSTEM COMPONENTS OF HEALTH AND INNOVATION FOR THE ORGANIZATION OF NANO-BIOMEDIC ECOSYSTEM TECHNOLOGICAL PLATFORM. Current Politics and Economics of Russia, Eastern and Central Europe, 34(2/3), 299-305.
108. Radford, S. J., Go, A. M. M., & McKim, K. S. (2017). Cooperation between kinesin motors promotes spindle symmetry and chromosome organization in oocytes. Genetics, 205(2), 517-527.
109. Rafelski, S. M., Viana, M. P., Zhang, Y., Chan, Y. H. M., Thorn, K. S., Yam, P., ... & Marshall, W. F. (2012). Mitochondrial network size scaling in budding yeast. Science, 338(6108), 822-824.
110. Ramat, A., Hannaford, M., & Januschke, J. (2017). Maintenance of miranda localization in Drosophila neuroblasts involves interaction with the cognate mRNA. Current Biology, 27(14), 2101-2111.
111. Ranjan, R., Snedeker, J., & Chen, X. (2019). Asymmetric centromeres differentially coordinate with mitotic machinery to ensure biased sister chromatid segregation in germline stem cells. Cell stem cell, 25(5), 666-681.
112. Rebollo, E., Sampaio, P., Januschke, J., Llamazares, S., Varmark, H., & González, C. (2007). Functionally unequal centrosomes drive spindle orientation in asymmetrically dividing Drosophila neural stem cells. Developmental cell, 12(3), 467-474.
113. Render, J. (1989). Development of Ilyanassa obsoleta embryos after equal distribution of polar lobe material at first cleavage. Developmental biology, 132(1), 241-250.
114. Roubinet, C., & Cabernard, C. (2014). Control of asymmetric cell division. Current opinion in cell biology, 31, 84-91.
115. Roubinet, C., Tsankova, A., Pham, T. T., Monnard, A., Caussinus, E., Affolter, M., & Cabernard, C. (2017). Spatio-temporally separated cortical flows and spindle geometry establish physical asymmetry in fly neural stem cells. Nature communications, 8(1), 1383.
116. Saarikangas, J., Caudron, F., Prasad, R., Moreno, D. F., Bolognesi, A., Aldea, M., & Barral, Y. (2017). Compartmentalization of ER-bound chaperone confines protein deposit formation to the aging yeast cell. Current Biology, 27(6), 773-783.
117. Salina, D., Bodoor, K., Eckley, D. M., Schroer, T. A., Rattner, J. B., & Burke, B. (2002). Cytoplasmic dynein as a facilitator of nuclear envelope breakdown. Cell, 108(1), 97-107.
118. Sallé, J., Xie, J., Ershov, D., Lacassin, M., Dmitrieff, S., & Minc, N. (2019). Asymmetric division through a reduction of microtubule centering forces. Journal of Cell Biology, 218(3), 771-782.
119. Salzmann, V., Chen, C., Chiang, C. Y. A., Tiyaboonchai, A., Mayer, M., & Yamashita, Y. M. (2014). Centrosome-dependent asymmetric inheritance of the midbody ring in Drosophila germline stem cell division. Molecular biology of the cell, 25(2), 267-275.

120. Schuldt, A. J., Adams, J. H., Davidson, C. M., Micklem, D. R., Haseloff, J., St Johnston, D., & Brand, A. H. (1998). Miranda mediates asymmetric protein and RNA localization in the developing nervous system. Genes & development, 12(12), 1847-1857.
121. Shakiba, N., Li, C., Garcia-Ojalvo, J., Cho, K. H., Patil, K., Walczak, A., Liu, Y. Y., Kuehn, S., Nie, Q., Klein, A., Deco, G., Kringelbach, M., & Iyer-Biswas, S. (2022). How can Waddington-like landscapes facilitate insights beyond developmental biology?. Cell systems, 13(1), 4–9. https://doi.org/10.1016/j.cels.2021.12.003
122. Simon, C. S., Hadjantonakis, A. K., & Schröter, C. (2018). Making lineage decisions with biological noise: Lessons from the early mouse embryo. Wiley interdisciplinary reviews. Developmental biology, 7(4), e319. https://doi.org/10.1002/wdev.319
123. Skamagki, M., Wicher, K. B., Jedrusik, A., Ganguly, S., & Zernicka-Goetz, M. (2013). Asymmetric localization of Cdx2 mRNA during the first cell-fate decision in early mouse development. Cell reports, 3(2), 442-457.
124. Sousa-Nunes, R., Chia, W., & Somers, W. G. (2009). Protein phosphatase 4 mediates localization of the Miranda complex during Drosophila neuroblast asymmetric divisions. Genes & development, 23(3), 359-372.
125. Stanoev, A., & Koseska, A. (2022). Robust cell identity specifications through transitions in the collective state of growing developmental systems. Current Opinion in Systems Biology, 31, 100437.
126. Thayer, N. H., Leverich, C. K., Fitzgibbon, M. P., Nelson, Z. W., Henderson, K. A., Gafken, P. R., ... & Gottschling, D. E. (2014). Identification of long-lived proteins retained in cells undergoing repeated asymmetric divisions. Proceedings of the National Academy of Sciences, 111(39), 14019-14026.
127. Tkemaladze, J. (2025). Replicative Hayflick Limit. Longevity Horizons, 1(2). doi: https://doi.org/10.5281/zenodo.14752664
128. Tkemaladze, J. (2025). Anatomy, Biogenesis, and Role in Cell Biology of Centrioles. Longevity Horizons, 1(2). doi: https://doi.org/10.5281/zenodo.14742232
129. Tkemaladze, J. (2025). Concept to The Restoring Dogmas. Longevity Horizons, 1(1). doi: https://doi.org/10.5281/zenodo.14708980
130. Tkemaladze, J. (2025). The Epistemological Reconfiguration and Transubstantial Reinterpretation of Eucharistic Practices Established by the Divine Figure of Jesus Christ in Relation to Theological Paradigms. doi: http://dx.doi.org/10.13140/RG.2.2.28347.73769
131. Tkemaladze, J. (2025). Concept to The Caucasian Bridge. Longevity Horizons, 1(1). doi: https://doi.org/10.5281/zenodo.14689276
132. Tkemaladze, J. (2025). Concept to The Alive Language. Longevity Horizons, 1(1). doi: https://doi.org/10.5281/zenodo.14688792
133. Tkemaladze, J. (2025). Transforming the psyche with phoneme frequencies "Habere aliam linguam est possidere secundam animam" Charlemagne. doi: http://dx.doi.org/10.13140/RG.2.2.16105.61286
134. Tkemaladze, J. (2025). Concept to The Eternal Youth. Longevity Horizons, 1(1). doi: https://doi.org/10.5281/zenodo.14681902
135. Tkemaladze, J. (2025).Achieving Perpetual Vitality Through Innovation. doi: http://dx.doi.org/10.13140/RG.2.2.31113.35685
136. Tkemaladze, J. (2025). Concept to The Curing All Diseases. Longevity Horizons, 1(1). doi: https://doi.org/10.5281/zenodo.14676208
137. Tkemaladze, J. (2025). A Universal Approach to Curing All Diseases: From Theoretical Foundations to the Prospects of Applying Modern Biotechnologies in Future Medicine. doi: http://dx.doi.org/10.13140/RG.2.2.24481.11366
138. Tkemaladze, J. (2025). Strategic Importance of the Caucasian Bridge and Global Power Rivalries. doi: http://dx.doi.org/10.13140/RG.2.2.19153.03680
139. Tkemaladze, J. (2025). Concept to The Food Security. Longevity Horizons, 1(1). doi: https://doi.org/10.5281/zenodo.14642407
140. Tkemaladze, J. (2025).Systemic Resilience and Sustainable Nutritional Paradigms in Anthropogenic Ecosystems. doi: http://dx.doi.org/10.13140/RG.2.2.18943.32169/1
141. Tkemaladze, J. (2025). Concept to the Living Space. Longevity Horizons, 1(1). doi: https://doi.org/10.5281/zenodo.14635991
142. Tkemaladze, J. (2025). Solutions to the Living Space Problem to Overcome the Fear of Resurrection from the Dead. doi: http://dx.doi.org/10.13140/RG.2.2.34655.57768

143. Tkemaladze, J. (2025). The Concept of Data-Driven Automated Governance. Georgian Scientists, 6(4), 399–410. doi: https://doi.org/10.52340/gs.2024.06.04.38
144. Tkemaladze, J. (2024). Elimination of centrioles. Georgian Scientists, 6(4), 291–307. doi: https://doi.org/10.52340/gs.2024.06.04.25
145. Tkemaladze, J. (2024). The rate of stem cell division decreases with age. Georgian Scientists, 6(4), 228–242. doi: https://doi.org/10.52340/gs.2024.06.04.21
146. Tkemaladze, J. (2024). Absence of centrioles and regenerative potential of planaria. Georgian Scientists, 6(4), 59–75. doi: https://doi.org/10.52340/gs.2024.06.04.08
147. Tkemaladze, J. (2024). Main causes of intelligence decrease and prospects for treatment. Georgian Scientists, 6(2), 425–432. doi: https://doi.org/10.52340/gs.2024.06.02.44
148. Tkemaladze, J. (2024). Cell center and the problem of accumulation of oldest centrioles in stem cells. Georgian Scientists, 6(2), 304–322. doi: https://doi.org/10.52340/gs.2024.06.02.32
149. Tkemaladze, J., & Samanishvili, T. (2024). Mineral ice cream improves recovery of muscle functions after exercise. Georgian Scientists, 6(2), 36–50. doi: https://doi.org/10.52340/gs.2024.06.02.04
150. Tkemaladze J. Editorial: Molecular mechanism of ageing and therapeutic advances through targeting glycative and oxidative stress. Front Pharmacol. 2024 Mar 6;14:1324446. doi: 10.3389/fphar.2023.1324446. PMID: 38510429; PMCID: PMC10953819.
151. Tkemaladze, Jaba and Kipshidze, Mariam, Regeneration Potential of the Schmidtea Mediterranea CIW4 Planarian. Available at SSRN: https://ssrn.com/abstract=4633202 or http://dx.doi.org/10.2139/ssrn.4633202
152. Tkemaladze, J. (2023). Is the selective accumulation of oldest centrioles in stem cells the main cause of organism ageing?. Georgian Scientists, 5(3), 216–235. doi: https://doi.org/10.52340/2023.05.03.22
153. Tkemaladze, J. (2023). Cross-senolytic effects of dasatinib and quercetin in humans. Georgian Scientists, 5(3), 138–152. doi: https://doi.org/10.52340/2023.05.03.15
154. Tkemaladze, J. (2023). Structure and possible functions of centriolar RNA with reference to the centriolar hypothesis of differentiation and replicative senescence. Junior Researchers, 1(1), 156–170. doi: https://doi.org/10.52340/2023.01.01.17
155. Tkemaladze, J. (2023). The centriolar hypothesis of differentiation and replicative senescence. Junior Researchers, 1(1), 123–141. doi: https://doi.org/10.52340/2023.01.01.15
156. Tkemaladze, J. (2023). Reduction, proliferation, and differentiation defects of stem cells over time: a consequence of selective accumulation of old centrioles in the stem cells?. Molecular Biology Reports, 50(3), 2751-2761.
157. Tkemaladze, J. (2023). Long-Term Differences between Regenerations of Head and Tail Fragments in Schmidtea Mediterranea Ciw4. Available at SSRN 4257823.
158. Tkemaladze, J., & Apkhazava, D. (2019). Dasatinib and quercetin: short-term simultaneous administration improves physical capacity in human. J Biomedical Sci, 8(3), 3.
159. Tkemaladze, J., Tavartkiladze, A., & Chichinadze, K. (2012). Programming and Implementation of Age-Related Changes. In Senescence. IntechOpen.
160. Tkemaladze, J., & Chichinadze, K. (2010). Centriole, differentiation, and senescence. Rejuvenation research, 13(2-3), 339-342.
161. Tkemaladze, J. V., & Chichinadze, K. N. (2005). Centriolar mechanisms of differentiation and replicative aging of higher animal cells. Biochemistry (Moscow), 70, 1288-1303.
162. Tkemaladze, J., & Chichinadze, K. (2005). Potential role of centrioles in determining the morphogenetic status of animal somatic cells. Cell biology international, 29(5), 370-374.
163. Toledo-Jacobo, L., Henson, J. H., & Shuster, C. B. (2019). Cytoskeletal polarization and cytokinetic signaling drives polar lobe formation in spiralian embryos. Developmental biology, 456(2), 201-211.
164. Tozer, S., Baek, C., Fischer, E., Goiame, R., & Morin, X. (2017). Differential routing of Mindbomb1 via centriolar satellites regulates asymmetric divisions of neural progenitors. Neuron, 93(3), 542-551.
165. Tsankova, A., Pham, T. T., Garcia, D. S., Otte, F., & Cabernard, C. (2017). Cell polarity regulates biased myosin activity and dynamics during asymmetric cell division via Drosophila Rho kinase and protein kinase N. Developmental Cell, 42(2), 143-155.
166. Van De Rijn, M., Heimfeld, S., Spangrude, G. J., & Weissman, I. L. (1989). Mouse hematopoietic stem-cell antigen Sca-1 is a member of the Ly-6 antigen family. Proceedings of the National Academy of Sciences, 86(12), 4634-4638.

167. van Leen, E. V., Di Pietro, F., & Bellaïche, Y. (2020). Oriented cell divisions in epithelia: from force generation to force anisotropy by tension, shape and vertices. Current Opinion in Cell Biology, 62, 9-16.
168. Waddington CH (1957) The Strategy of the Genes: A Discussion of Some Aspects of Theoretical Biology
169. Walter, P., & Ron, D. (2011). The unfolded protein response: from stress pathway to homeostatic regulation. science, 334(6059), 1081-1086.
170. Wang, J., Wang, L., Feng, G., Wang, Y., Li, Y., Li, X., ... & Zhou, Q. (2018). Asymmetric expression of LincGET biases cell fate in two-cell mouse embryos. Cell, 175(7), 1887-1901.
171. Wang, X., Tsai, J. W., Imai, J. H., Lian, W. N., Vallee, R. B., & Shi, S. H. (2009). Asymmetric centrosome inheritance maintains neural progenitors in the neocortex. Nature, 461(7266), 947-955.
172. Weinmaster, G., & Fischer, J. A. (2011). Notch ligand ubiquitylation: what is it good for?. Developmental cell, 21(1), 134-144.
173. Wheat, J. C., Sella, Y., Willcockson, M., Skoultchi, A. I., Bergman, A., Singer, R. H., & Steidl, U. (2020). Single-molecule imaging of transcription dynamics in somatic stem cells. Nature, 583(7816), 431–436. https://doi.org/10.1038/s41586-020-2432-4
174. Winkley, K., Ward, S., Reeves, W., & Veeman, M. (2019). Iterative and complex asymmetric divisions control cell volume differences in Ciona notochord tapering. Current Biology, 29(20), 3466-3477.
175. Wooten, M., Ranjan, R., & Chen, X. (2020). Asymmetric histone inheritance in asymmetrically dividing stem cells. Trends in Genetics, 36(1), 30-43.
176. Wooten, M., Snedeker, J., Nizami, Z. F., Yang, X., Ranjan, R., Urban, E., ... & Chen, X. (2019). Asymmetric histone inheritance via strand-specific incorporation and biased replication fork movement. Nature structural & molecular biology, 26(8), 732-743.
177. Xie, J., Wooten, M., Tran, V., Chen, B. C., Pozmanter, C., Simbolon, C., ... & Chen, X. (2015). Histone H3 threonine phosphorylation regulates asymmetric histone inheritance in the Drosophila male germline. Cell, 163(4), 920-933.
178. Yamashita, Y. M., Mahowald, A. P., Perlin, J. R., & Fuller, M. T. (2007). Asymmetric inheritance of mother versus daughter centrosome in stem cell division. Science, 315(5811), 518-521.
179. Yu, F., Morin, X., Cai, Y., Yang, X., & Chia, W. (2000). Analysis of partner of inscuteable, a novel player of Drosophila asymmetric divisions, reveals two distinct steps in inscuteable apical localization. Cell, 100(4), 399-409.
180. Zhang, F., Huang, Z. X., Bao, H., Cong, F., Wang, H., Chai, P. C., ... & Yang, X. (2016). Phosphotyrosyl phosphatase activator facilitates localization of Miranda through dephosphorylation in dividing neuroblasts. Development, 143(1), 35-44.
181. Zhou, C., Slaughter, B. D., Unruh, J. R., Guo, F., Yu, Z., Mickey, K., ... & Li, R. (2014). Organelle-based aggregation and retention of damaged proteins in asymmetrically dividing cells. Cell, 159(3), 530-542.Chichinadze, K., Lazarashvili, A., & Tkemaladze, J. (2013). RNA in centrosomes: structure and possible functions. Protoplasma, 250(1), 397-405.
182. Прангишвили, А. И., Гаситашвили, З. А., Мацаберидзе, М. И., Чичинадзе, К. Н., Ткемаладзе, Д. В., & Азмайпарашвили, З. А. (2017). К топологии антитеррористических и антикриминальных технологии для образовательных программ. В научном издании представлены материалы Десятой международной научно-технической конфе-ренции «Управление развитием крупномасштабных систем (MLSD'2016)» по следующим направле-ниям:• Проблемы управления развитием крупномасштабных систем, включая ТНК, Госхолдин-ги и Гос-корпорации., 284.
183. Прангишвили, А. И., Гаситашвили, З. А., Мацаберидзе, М. И., Чхартишвили, Л. С., Чичинадзе, К. Н., & Ткемаладзе, Д. В. (2017). & Азмайпарашвили, ЗА (2017). Системные составляющие здравоохранения и инноваций для организации европейской нано-биомедицинской екосистемной технологической платформы. Управление развитием крупномасштабных систем MLSD, 365-368.
184. Ткемаладзе, Д. (2025). Репликативный Лимит Хейфлика. doi: http://dx.doi.org/10.13140/RG.2.2.25803.30249
185. Ткемаладзе, Д. (2025). Дифференциация соматических клеток многоклеточных животных. doi: http://dx.doi.org/10.13140/RG.2.2.23348.97929
186. Ткемаладзе, Д. (2025). Анатомия, биогенез и роль в клеточной биологии центриолей. doi: http://dx.doi.org/10.13140/RG.2.2.27441.70245
187. Ткемаладзе, Д. В., & Чичинадзе, К. Н. (2005). Центриолярные механизмы дифференцировки и репликативного старения клеток высших животных. Биохимия, 70(11), 1566-1584.

188. Ткемаладзе, Д., Цомаиа, Г., & Жоржолиани, И. (2001). Создание искусственных самоадаптирующихся систем на основе Теории Прогноза. Искусственный интеллект. УДК 004.89. Искусственный интеллект. УДК 004.89.
189. Чичинадзе, К., Ткемаладзе, Д., & Лазарашвили, А. (2012). НОВЫЙ КЛАСС РНК И ЦЕНТРОСОМНАЯ ГИПОТЕЗА СТАРЕНИЯ КЛЕТОК. Успехи геронтологии, 25(1), 23-28.
190. Чичинадзе, К. Н., & Ткемаладзе, Д. В. (2008). Центросомная гипотеза клеточного старения и дифференциации. Успехи геронтологии, 21(3), 367-371.

