Breaking symmetry: the asymmetries in epigenetic inheritance

Symmetry and asymmetry are the fundamental aspects of life. Most cells within a multicellular organism contain the same genetic information, passed on from one originating cell, the zygote; however, these cells can take on a variety of different identities, with diverse appearances and functions. A fundamental question in biology ponders how cells containing identical DNA content can take on different cell identities. Epigenetic mechanisms could be the symmetry-breaking factor, as they are able to change the gene expression in cells without changing the DNA sequence. While the process of duplication and segregation of DNA during cell division has been well studied, it is less understood how the epigenetic information is established and inherited in the cells within a multicellular organism. Studies of asymmetric stem cell division, where a stem cell division gives rise to a self-renewed stem cell and a differentiating daughter cell, provide a model to study how epigenetic information is maintained or changed to produce daughter cells with identical genetic information but distinct cell fates. Here, we discuss the findings and ideas of how epigenetic information is maintained or changed during asymmetric cell division and the importance of this asymmetry in influencing cell fate.

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Interplay between symmetry and asymmetry as the basis of life

The concept of symmetry is rooted deep within nature and governs the laws of physics that describe the world around us. In biology, symmetry can be observed within the complex organization of structures, such as in the body patterning of many multicellular organisms including humans, as well as within the individual cells that compose them. Most cells within an organism contain identical genetic information, making them inherently symmetric.

Every metazoan multicellular organism originates from one cell, a fertilized egg, containing the genetic information from both mother and father, that must be copied and passed on to all of the cells within the organism. This is achieved through the processes of DNA replication and cell division, where the genetic information of a cell is faithfully copied and segregated to the two resulting daughter cells. These processes at the core are inherently symmetric and can give rise to two identical cells; however, not all cells within an organism are the same. For example, within the human body, there are more than 200 different cell types and each of them have unique appearances and carry out specific functions. Thus, a fundamental question to understanding the complexity of a multicellular organism is how cells can become different while containing the same genetic information.

As most cells in an organism contain the same DNA sequences, their differences arise in how this genetic information is utilized. While the genetic information contains all of the DNA sequences necessary for the development and maintenance of an organism, each cell only expresses a subset of these sequences in a spatiotemporally specific manner, i.e., in the right place with the appropriate timing and at the proper level. Different cell types are thus determined by these distinct gene expression programmes that are regulated by epigenetics. Epigenetic mechanisms are heritable changes in gene expression that do not change the DNA sequence. Epigenetic mechanisms could be the symmetry-breaking factors that are able to change the gene expression without changing the DNA sequence.

One method of regulating gene expression is through the modification of chromatin states. Chromatin consists of DNA and the tightly associated proteins called histones. Histones can be post-translationally modified to affect the wrapping and thus accessibility of DNA, which subsequently affects gene expression in different regions of the genome. During cell division, epigenetic information must be passed along to the daughter cells,
Breaking Symmetry

resembling a ‘cellular memory’. While it is well studied how the genetic information is faithfully copied and partitioned during cell division, it is largely unclear how epigenetic states are established and inherited.

To understand how epigenetic states are maintained or changed during cell division to give rise to the wide variety of cell types within an organism, researchers have turned to studying the process of asymmetric cell division. This mode of cell division is often used by stem cells to produce two genetically identical daughter cells that take on distinct cell fates, one self-renewed stem cell and one differentiating daughter cell (Figure 1). This process provides a great opportunity to study how epigenetic information is inherited to give rise to two different cells at a single-cell level. The study of epigenetic inheritance during asymmetric stem cell division offers insights into how the baseline symmetry can be ‘broken’ to give rise to the cellular diversity observed within a multicellular organism.

**Breaking symmetry through asymmetric inheritance in the chromatin context**

Epigenetic inheritance begins at chromatin. The chromatin configuration at a particular gene locus will directly affect whether or not that gene is expressed. Open and accessible chromatin, known as euchromatin, is associated with active gene expression, while tightly condensed chromatin, referred to as heterochromatin, is associated with gene silencing. This local chromatin environment can be modulated by changing the interaction between the DNA and the associated histone proteins. When a cell is preparing to divide, it first undergoes DNA replication, which is a semi-conservative process. During this process, the double-stranded parental DNA separates into two template strands, which are both used to synthesize a new complimentary strand, giving rise to two completely identical daughter DNA strands containing the same genetic information. During DNA replication, the chromatin structure must be disassembled for the duplicating process of the DNA strand and then reassembled onto the two new DNA strands, forming what are known as sister chromatids. As these sets of sister chromatids will be inherited by the resulting daughter cells, this process provides an opportunity to establish different chromatin states that will be asymmetrically inherited.

Histones serve as a major carrier of epigenetic information. Understanding how histones are inherited during asymmetric cell division gives insight into how epigenetic information is maintained or changed to give rise to daughter cells with different identities. In the case...
Breaking Symmetry

of *Drosophila* male germline stem cells, which undergo asymmetric cell division, histones are asymmetrically segregated based on age, where old, pre-existing histones are preferentially inherited by the self-renewed stem cell and newly synthesized histones are segregated to the daughter cell that will go on to differentiate into sperm. It is thought that the old histones contain an ‘epigenetic memory’ that is inherited by the renewed stem cell, allowing it to continue the stem cell gene expression programme and therefore stem cell fate. In contrast, newly synthesized histones do not have this epigenetic memory, which allows for the inheriting cell to establish a new gene expression profile and new cell identity, different from its mother cell.

In order for this asymmetric inheritance of epigenetic information to occur, the old and new histone proteins must be first asymmetrically incorporated into newly synthesized sister chromatids, and these epigenetically distinct sister chromatids need to be subsequently segregated asymmetrically to the two daughter cells. During DNA replication, it is necessary for the old, parental histones to be disassembled from the DNA to allow the replication machinery to proceed with DNA synthesis without hindrance. Recent work has demonstrated that the replication machinery components can also serve as histone chaperones, aiding the reassembly of histones onto the newly synthesized strands. The recycled parental histones along with newly synthesized histones together fulfill the need for twice the number of histones that are used to populate the two sister chromatids. By biasing to which sister chromatid the parental and newly synthesized histones are shuttled on to, an asymmetric distribution between old and new histones can be formed. This process contributes to the formation of epigenetically distinct sister chromatids (Figure 2).

During cell division, the process of mitosis must differentially recognize the two sets of sister chromatids and properly segregate them to the resulting daughter cells. This process involves opposing subcellular structures referred to as centrosomes that emanate microtubules that attach to specific areas of the sister chromatids, known as centromeres, and pull them in opposite directions to the daughter cells. In asymmetric cell division, there are both cis-factors within sister chromatids and trans-factors from the mitotic machinery that work together to ensure that epigenetically distinct sister chromatids are properly segregated to the daughter cells. The cis-factors are within the sister chromatids, such as the centromeres. Centromeres are defined by a histone variant protein, CENP-A. It has been discovered that sister chromatids can carry different amounts of CENP-A, leading to asymmetric sister centromeres that can bias microtubule attachment during mitosis. In *Drosophila* germline stem cells, the sister chromatids with ‘stronger’ centromeres containing more CENP-A proteins are preferentially inherited by the self-renewed stem cell, serving as a mechanism to recognize and segregate epigenetically distinct sister chromatids. During asymmetric cell division, there is temporal activation of the centrosomes where one centrosome becomes active first, emanating microtubules that break down the nuclear envelope on one side and preferentially

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**Figure 2.** The two-step process of asymmetric epigenetic inheritance. Asymmetric sister chromatids are formed after DNA replication as histones are incorporated into the newly synthesized sister chromatids. During this process, old and new histones are incorporated asymmetrically into the sister chromatids. Further, the DNA methylation pattern must be re-established on the newly synthesized DNA, creating an opportunity to establish asymmetric methylation patterns. Further, these epigenetically distinct sister chromatids must be asymmetrically segregated to the resulting daughter cells. This is achieved through the recognition of asymmetric sister centromeres by asymmetric microtubule activity coordinated by the centrosomes.
Breaking Symmetry

Attach to the sister chromatids containing the ‘stronger’ centromeres. Together, asymmetric centrosome activity, nuclear envelope breakdown and differential microtubule attachment to asymmetric sister centromeres co-ordinate to allow for preferential inheritance of epigenetically distinct sister chromatids, leading to the asymmetric epigenetic inheritance during this atypical mitosis called asymmetric cell division (Figure 2).

In addition to histones and their modifications, chromatin contains other sources of epigenetic information. For example, DNA methylation refers to the addition of a methyl group onto a cytosine base (5mC) in DNA, which is a heritable mark that also influences gene expression. During DNA replication, the 5mC mark would need to be copied onto the newly synthesized strands, which could provide an opportunity to establish asymmetric methylation patterns on sister chromatids. Detectable differences in DNA methylation between sister chromatids has been reported in stem cells, with the highest asymmetry observed in pluripotent mouse blastocysts. This asymmetry could be achieved by repressing maintenance DNA methylases or affecting the demethylation process in a biased manner. Thus, DNA methylation may be asymmetrically inherited to influence the epigenetic states and possibly gene expression within the resulting cells.

Breaking symmetry through asymmetric inheritance of factors outside of chromatin

During cell division, the parent cell must segregate the genetic information to both daughter cells, as well as divide up the cytoplasmic components, including various RNAs, proteins and organelles. While the chromatin states inherited by the daughter cells will play a large role in establishing cell identity, cytoplasmic factors can also affect cell fate decisions.

Many cytoplasmic components are segregated in an unequal manner during asymmetric cell division. One such example is the polarity proteins, including the Par complex...
proteins, which influence mitotic spindle orientation and aid in segregating other cell fate determinants. These asymmetrically inherited cell fate determinants could also influence gene expression and function in the inheriting daughter cells. Further, RNA-binding proteins such as Staufen can be partitioned unequally along with their cargo mRNAs. In the case of Staufen, the inherited mRNAs will produce proteins that promote a differentiation programme and suppress the stem cell fate. Additionally, mRNAs can be inherited asymmetrically through their association with RNA granules, such as germ granules that directly influence the germline fate. The asymmetric inheritance of these cytoplasmic components promotes the adoption of a particular cell fate. In the case of Drosophila neuroblast division, the tumour suppressor proteins Numb and Brat are inherited asymmetrically to inhibit proliferation and promote differentiation. Here, asymmetric inheritance of cytoplasmic factors can influence cell identities in the inheriting cells (Figure 3).

**Disrupted asymmetric inheritance and the relationship with diseases**

The balance of asymmetric cell division is vital for development and homeostasis of an organism. Without this balance, if the life-originating zygote was only able to divide symmetrically, it would form a mass of identical cells rather than a diverse multicellular organism. The establishment and segregation of asymmetric cellular components could allow for cells to take on different gene expression programmes and therefore unique cell identities. Loss of this asymmetry could be detrimental to the organism, leading to scenarios such as overproliferation of stem cells and tumour formation, or loss of stem cells and tissue degeneration. Key regulators of asymmetric cell division are often found to be mutated or misexpressed in cancers. For example, loss of function of \( PARD6 \) and \( PARD3 \), which encode the human Par complex polarity proteins \( \text{Par6} \) and \( \text{Par3} \), respectively, has been identified in lung, head, neck, oesophagus, prostate and bladder cancers. Thus, the balance of asymmetric cell division is vital for proper tissue and organism homeostasis.

Epigenetic mechanisms were first linked to cancers by the connection between abnormal changes in DNA methylation and instances of cancer. For example, a hypermethylated promoter region of tumour suppressor genes could lead to their compromised expression, which could contribute to tumorigenesis upon cell division and the transmission of such an epigenetic status. Since then, many different epigenetic cell division is vital for proper tissue and organism homeostasis.

Epigenetic mechanisms were first linked to cancers by the connection between abnormal changes in DNA methylation and instances of cancer. For example, a hypermethylated promoter region of tumour suppressor genes could lead to their compromised expression, which could contribute to tumorigenesis upon cell division and the transmission of such an epigenetic status. Since then, many different epigenetic mechanisms have been revealed to be abnormal in various types of cancer. For histone proteins, misregulated post-translational modifications, including incorrect modifications, modifications at the wrong regions and inappropriate levels of modifications, have been found in tumour cells. Recently, mutations in histone genes themselves have also been identified in a variety of human cancers, termed ‘oncohistone’ mutations. These oncohistones often act in a ‘dominant’ manner that could affect normal histone protein functions. Therefore, misregulation of histone proteins and their post-translational modifications can drastically influence gene expression profiles through the loss or change of proper epigenetic information for normal cellular functions (Figure 4). This misregulation of the epigenetic information can cause changes in cell identity and lead to diseases such as cancer and tissue dystrophy, as well as failures in tissue repair and regeneration.

**Conclusions and perspectives**

A long-standing question in biology has been how the inherently symmetric process of DNA replication and
cell division is able to give rise to the diverse set of cells found in a multicellular organism. Recent studies demonstrate that epigenetic states could serve as one symmetry-breaking factor, which allow for cells with identical genetic information to express different subsets of genes in a spatiotemporally controlled manner and take on distinct cell fates. Current research has demonstrated that the inherently symmetric processes of both DNA replication and cell division can have biases that lead to asymmetric establishment and segregation of epigenetic information. During such an asymmetric cell division, there is a complex network of molecular mechanisms and cellular components that contribute to asymmetric chromatin states between sister chromatids, followed by their asymmetric inheritance into the resulting daughter cells. These processes subsequently allow the daughter cells to adopt different cell fates. Thus, asymmetric epigenetic inheritance serves as a way to break the inherent symmetry of life, contributing to the cellular diversity observed in multicellular organisms.

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Further Reading

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