Cell Cycle

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Contributor: Zhixiang Wang

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cell cycle History Phase

1. Introduction

The cell cycle, or the cell division cycle, is the series of events that take place in a cell that drive it to divide and produce two new daughter cells. The typical cell cycle in eukaryotes is composed of four phases including the G1, S, G2, and M phase. G1, S, and G2 together are called interphase. M phase is comprised of mitosis, in which the cell's nucleus divides, and cytokinesis, in which the cell's cytoplasm divides to form two daughter cells. Mitosis and cytokinesis are tightly coupled together. Mitosis is further divided into five subphases including prophase, prometaphase, metaphase, anaphase, and telophase. Each phase of cell cycle progression is reliant on the proper completion of the previous cell cycle phase. A cell could also exit from cell cycle to enter G0 phase, a state of quiescence [1][2].

Cell cycle progression is mediated by cyclin-dependent kinases (Cdks) and their regulatory cyclin subunits. Cdks, such as Cdk4/6, Cdk2, and Cdk1 (also known as Cdc2) are serine/threonine kinases with a wide variety of substrates. Cdks are activated mainly by binding to their cyclin partners, whose expressions rise and fall throughout the cell cycle to mediate the temporal activation of each Cdks. Various cell cycle checkpoints exist to ensure that critical processes are engaged prior to progression to the next phase. There are three major cell cycle checkpoints, including the G1/S checkpoint (also referred as restriction point), the G2/M DNA damage checkpoint, and the spindle assembly checkpoint (SAC) [3][4][5].

2. Early History of Cell Cycle Discovery

Cell theory was developed in the middle of the 19th century. This theory has three main components: (1) Every living organism is composed of one or more cells; (2) cells are the basic unit of life for all living organisms, and (3) cells only arise from pre-existing cells. While the first two components were the contribution of Theodor Schwann and Matthias Jakob Schleiden, the last is the contribution of German scientist and physician Rudolf Virchow. His discovery that all cells arise from pre-existing cells is the start point of cell cycle research [6][7][8].

At the turn of the 19th century to 20th century, the cell cycle has been the subject of intense study. The cytology of cell division is described in great detail by microscopists and embryologists, however, the underlying mechanisms driving cell division are mostly unknown. In the late 1970s and 1980s, the advancement of modern molecular biology provided means and knowledge to study the molecular mechanisms regulating cell cycle. Cell biologists, biochemists, and geneticists joined forces and demonstrated that the basic processes and control mechanisms of cell cycle are universal in eukaryotes.

In the late 19th century, early light microscopic studies recognized that cell division follows mitosis, during which cells condensed their chromosomes. Based on his observations of cell division in various stages, German biologist and a founder of cytogenetics Walther Flemming identified the sequence of chromosome movements in mitosis. Flemming's discovery was proven correct decades later by the study of live dividing cells [9]. However, the only observable morphological changes outside of mitosis is the growth of the cell size. Interphase remained a black box and recognized as one phase until the discovery that DNA synthesis occurs only in a short period during interphase [10]. This discovery split interphase into three phases: This DNA synthesis period is termed as S phase, the gap between mitosis and S phase is termed G1 phase, and the gap between S and M phases is termed as G2 phase [11].

Following the recognition of four major cell cycle states G1, S, G2, and M, the focus of cell cycle study shifted to understand the transition between these phases. A major task is to identify the factors driving the transition. In the early 1970s, by fusing cells at different stages of the cell cycle, it was shown that late G2 or M phase cells contained an M phase-promoting factor (MPF) capable of accelerating the onset of mitosis in early G2 cells [12]. It was further shown that S phase cells contains an S phase-promoting factor (SPF) in nuclei, which is able to accelerate S phase [12][13].

While there is no biochemical method available to purify either MPF or SPF at the time, genetic studies of cell cycle related genes are fruitful. At the end of the 1960s, Leland Hartwell realized the possibility of using genetic methods to study cell cycles. He established budding yeast *Saccharomyces cerevisiae* as a highly suitable model system to study cell cycles. In an elegant series of experiments in 1970–1971, he used the temperature sensitive lethal mutants of *S. cerevisiae* to isolate yeast cells with mutated genes, controlling the cell cycle. By this approach, he successfully identified more than one hundred genes which specifically involved in cell cycle control. Among these genes are genes encoding SPF and MPF. Hartwell named these genes Cdc-genes (cell division cycle genes) [14][15][16]. One particularly important gene identified is Cdc28, which controls the first step of cell cycle progression in G1 phase and was also known as "start".

In the middle of the 1970s, Paul Nurse followed Hartwell's approach to study cell cycle regulation with similar genetic methods but using fission yeast *Schizosaccharomyces pombe* as a model system. Through this research, Paul Nurse discovered the gene Cdc2 in fission yeast. Cdc2 is identical to Cdc28 identified in budding yeast. Nurse found that Cdc2 had a key function in the control of transition from G2 to mitosis during cell cycle [17]. In 1987, Nurse isolated the human version of Cdc2 gene, Cdk1. Cdk1 encodes a protein called cyclin-dependent kinase (Cdk). They found that phosphorylation status of the mammalian Cdc2 protein (p34Cdc2) is closely related to cell

cycle progression. It is phosphorylated when cells are stimulated to enter the cell cycle in G1 phase, but dephosphorylated when cells go to quiescence [18][19]. Based on these findings, half a dozen different Cdk molecules have been found in humans.

In the early 1980s, Tim Hunt discovered the first cyclin molecule by studying sea urchins, Arbacia. There are eight very rapid cell divisions during the cleavage in embryos of the sea urchin. To sustain these cell divisions, the continual protein synthesis is required. Hunt found that one protein is always destroyed each time the cells divide. This protein was named cyclin as the level of the protein vary periodically during the cell cycle [20]. In the following years, more cyclins were identified in various species by Hunt and other groups. Moreover, it was discovered that the cyclins bind to the Cdk molecules to regulate the Cdk activity and determine the substrate specificity of Cdks [21].

Another important concept introduced during this period is "Checkpoint". In the late 1980s, by studying the sensitivity of yeast cells to irradiation, Hartwell developed concept of checkpoint [22][23]. He observed that the cell cycle is arrested at certain point when DNA is damaged. This cell cycle checkpoint concept is then expanded as surveillance mechanisms used by the cells to check the integrity, fidelity, and the sequences of the major cell cycle events. The events being monitored include cell size growth, DNA replication, and integrity, and the accurate chromosome segregation [3].

The historical contribution of Leland H. Hartwell, Paul M. Nurse, and R. Timothy (Tim) Hunt earned them 2001 Nobel Prize in Physiology or Medicine for their discovery of "key regulators of the cell cycle".

3. Cell Cycle Progression through Various Phases

The cell cycle consists of G1, S, G2, and M phases. In G1 phase, the cell grows and becomes larger. The cell enters S phase when it reaches a certain size. S phase is the period for DNA-synthesis, during which the cell duplicates its DNA. In the following G2 phase, the cell monitors the completion of DNA-replication and prepares for mitosis. Chromosome segregation and cell division are completed in M phase. The proper cell cycle progression ensures that each of the two daughter cells receives identical chromosome from parent cell. After cell division, the cell cycle is completed, and the cells are back in G1 phase. The duration of the cell cycle varies between 10 and 30 h in most mammalian cells. Cells in the G1 can exit from the cell cycle and enter G0 phase, a state of quiescence.

Cell cycle progression is mainly driven and regulated by two classes of proteins, Cdks and cyclins [24]. In yeast, while several Cdks are expressed, including Cdk1, PHO85, and Kin28, only Cdk1 directly regulates cell cycle progression. Cdk1 is equivalent to p34Cdc2 in *S. pombe* and p34Cdc28 in *S cerevisiae*. By associating with different cell-cycle stage-specific cyclins Cdk1 regulates diverse cell cycle transitions including G1 to S transition and G2 to M transition. The roles of PHO85 and Kin28 in cell-cycle regulation are indirect [24][25]. Higher organisms possess many yeast Cdk1 functional homologues. These functional homologues are phase-specific Cdks. Each phase-specific Cdk acts in a specific cell phase to perform the function of Cdk1 in yeast. Approximately 20 Cdk-related proteins are discovered, which leads to the concept that cell cycle events in higher eukaryotic cells are

regulated by complex combinations of Cdks and cyclins in various cell cycle phases. For Cdk/cyclin complexes, cyclins confer substrate specificity and determine the regulatory consequence of the substrates such as activation, inactivation, and localization. Based on this hypothesis, the classical model of cell cycle regulation is established through extensive research in eukaryotic cells.

According to this model, Cdk4 and/or Cdk6 form complexes with D-type cyclins, which activates Cdk4/6 and initiates phosphorylation of the retinoblastoma protein (Rb) family in early G1 phase [26][27]. Rb phosphorylation stimulates the release of transcription factor E2F, which then stimulates the transcription of early E2F responsive genes required for the progression of the cell cycle [28][29]. Early E2F responsive genes include A- and E-type cyclins [26][30]. In the late G1 phase, cyclin E binds to and activate Cdk2, which leads to the full Rb phosphorylation and the further activation of E2F mediated transcription [26][27]. Together, the above events drive the passage of the cell through the restriction point at the boundary of the G1/S phase and initiate the S phase. At the onset of the S phase, A-type cyclins are synthesized and form complex with Cdk2, which phosphorylates proteins involved in DNA replication and drive the cell progression to G2 phase [31][32]. At the late G2 phase, Cdk1/cyclin A is formed and activated, which is required for the G2/M transition and the initiation of prophase [33]. Finally, Cdk1/cyclin B complexes are formed in M phase and drive the completion of mitosis [34].

3.1. G1 Phase

Cells enter G1 either from the preceding M phase or from G0 phase. The transition of cells between G0 and G1 phase is determined by extracellular mitogenic signals [35][36]. G1 phase is the growth phase. The biosynthetic activities of the cell are slowed down considerably in M phase; however, it resumes at a high rate in G1 phase. In G1 phase, the cells synthesize many proteins, amplify organelles including ribosomes and mitochondria, and grow in size. The duration of cell cycle phases varies considerably in different types of cells. For a typical proliferating human cell, if we assume the total cycle time is 24 h, the duration of G1 phase is approximately 11 h, S phase duration last 8 h, G2 phase last 4 h, and the duration of M phase is approximately 1 h.

During G1 phase, diverse signals, including environmental cues, stress, and metabolic cues intervene to influence cell’s developmental program. These signals are integrated and interpreted by the cells. Based on these inputs, the cell decides whether to self-renew, differentiate, or die; however, to enter S phase for starting its renewal, all cells must fulfill one essential requirement: activation of Cdks [36][37].

3.2. S Phase

S phase is marked by DNA synthesis. In S phase, each chromosome consists of two sister chromatids following replication to double the amount of DNA. However, S phase also marked with low activities of gene expression and protein synthesis. A noticeable exception is the production of histone. Most histones are produced in the S phase [38].

It is suggested that an intra-S phase checkpoint exists to control S phase progression. Intra-S phase checkpoint turns off Cdk2 in response to DNA damage and other replication stress, which blocks origin firing to avoid

replication of damaged DNA [39]. S phase to G2 phase transition is regulated by the active checkpoint kinase ATR (ataxia-telangiectasia and Rad3-related) [40].

3.3. G2 Phase

The cell enters G2 phase after successful completion of S phase. G2 phase ends with the onset of mitosis. The major task of cells in G2 phase is to prepare itself for mitosis. G2 phase is marked by significant protein/lipid synthesis and cell growth [41]. While it is known that protein synthesis inhibitor arrests cells at G2 phase, a recent study suggests that this may be due to the inhibition of p38, and the protein synthesis is not absolutely required for mitosis entry [42]. Interestingly, some cell types, including certain cancer cells and *Xenopus* embryos, lack the G2 phase. Cell cycle proceeds directly from S phase to M phase. It is hypothesized that cell size controls the growth in G2 phase, however, this is only demonstrated in fission yeast [43]. Another process that occurs during G2 phase is to repair DNA double-strand breaks. During and after DNA replication, DNA double-strand breaks accumulate in the cell and need to be repaired before cell can move to pass G2/M checkpoint [22][44][45].

3.4. Mitosis and Cytokinesis

M phase is comprised of mitosis, in which the cell's nucleus divides, and cytokinesis, in which the cell's cytoplasm divides to form two daughter cells. Mitosis is further divided into prophase, prometaphase, metaphase, anaphase, and telophase.

Prophase is characterized with chromatin/chromosome condensation, centrosome separation, and nuclear membrane breakdown. The migration of centrosome to two opposite poles is important for the later formation of the bipolar mitotic spindle apparatus. A recent detailed study shows that the interphase organization is rapidly lost in prophase by a condensin-dependent manner [46]. Observations with a microscope indicate that chromosomes become recognizable as linearly organized structures in early prophase [47]. Sister chromatids are mixed in early prophase, but they are separated in late prophase. Each chromatid is shown as an array of loops radiating from an axial core that contains topoisomerase II alpha and condensin complexes [48]. The rise of cyclin B-Cdk1 activity is a defining molecular event of prophase [49].

Prometaphase starts from the nuclear envelope breakdown, which marks the end of prophase, ends when chromosome alignment at the spindle equator completes, which defines the beginning of metaphase. For faithful chromosome segregation, it is essential to establish a metaphase plate in which all chromosomes aligned at the cell equator attach to mitotic spindle microtubules. The achievement of this configuration depends on the precise coordination of several mitotic events including nuclear envelope breakdown, connection between chromosome kinetochores, and microtubules of the mitotic spindle assembly, and the congression of all chromosomes to the spindle equator. A kinetochore is a disc-shaped protein structure in duplicated chromatids [50]. During prometaphase the chromatids shorten and become thicker [47] and ultimately form fully condensed metaphase chromosomes [51].

Metaphase starts when the duplicated chromosomes are aligned along the metaphase plate in the middle of the cell. During metaphase, the sister chromatids are pulled back and forth by the kinetochore microtubules until they align along the equatorial plane. The chromosome segregation process is monitored by SAC pathway to ensures that all kinetochores are attached to microtubules of the opposite poles before segregation proceeds after metaphase-to-anaphase transition. Once all the chromosomes are properly aligned and the kinetochores are correctly attached, the cohesion between sister chromatids is dissolved, leading to the migration of the separated chromatids towards opposite sides of the cell by the pulling force of spindle microtubules. The cell now enters the anaphase [52].

Anaphase involves two mechanistically distinct steps, the shortening of kinetochore microtubules and the spindle elongation in the midzone. The shortening of kinetochore microtubules causes the migration of each chromatid towards its respective pole. The disjointed sister chromatids are further separated through spindle elongation in the midzone. These two steps may be temporally divided in some organisms while occurring simultaneously in other organisms. These two steps are called anaphase A and anaphase B, respectively [53]. In human mitotic cells, anaphase B usually starts 30–50 s later than the start of the anaphase A [44][54]. During anaphase, the spindle elongates 8 µm and additional 3 µm in telophase [44][53].

Telophase follows anaphase and starts at the onset of the chromosome recondensation and the nuclear envelope reformation [45]. During telophase the duplicated chromosomes in the nucleus of a parent cell separate into two identical daughter cells. A nuclear membrane forms around each set of chromosomes to divide the nuclear DNA from the cytoplasm. Simultaneously, the chromosome decondensation begins [53].

Cytokinesis results the physical separation of the cytoplasm of a mother cell into two daughter cells [55][56]. The segregation of chromosomes and cytoplasm needs to be tightly coordinated to generate offspring with the right complement of chromosomes [57]. Cell cytokinesis is initiated in anaphase, when lower Cdk1 activity causes the reorganization of the mitotic spindle and the stabilization of microtubules. The assembly of the central spindle is the key early event, which provides the template for the midbody and contributes to division plane specification. The division plane is positioned between the two sets of segregated chromosomes. The precise position of the plane is critical to prevent segregation errors. Cytokinetic furrow ingression of the attached plasma membrane is then initiated by the contraction of the actomyosin ring, which partitions the cytoplasm into two domains of emerging daughter cells. The last step of cytokinesis is abscission [58]. Abscission is the physical separation of the plasma membrane of the two daughter cells. During abscission, cells remove the cytoskeletal structures from the intercellular bridge, followed by constriction of the cell cortex, and finally the division of the plasma membrane [59][60].

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