4 Control of the Cell Cycle

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SUMMARY OF KEY POINTS

- Cells in most postnatal tissues are quiescent. Exceptions include cells of the hematopoietic system, skin, and gastrointestinal mucosa.
- The key challenges for proliferating cells are to make an accurate copy of the 3 billion bases of DNA (S phase) and to segregate the duplicated chromosomes equally into daughter cells (mitosis).
- Progression through the cell cycle is dependent on both extrinsic and intrinsic factors.
- Extrinsic factors include cell-to-cell contact, basement membrane attachments, and growth factor or cytokine exposure.
- The internal cell cycle machinery is controlled largely by oscillating levels of cyclin proteins and by modulation of cyclin-dependent kinase activity.
- One way in which growth factors regulate cell cycle progression is by affecting the levels of the D-type cyclins in the G_1 phase of the cell cycle.
- The restriction point of the cell cycle occurs in late G_1 and is the point beyond which the cell is committed to progress through the rest of the cell cycle. It is governed by a known tumor suppressor, the retinoblastoma protein.
- Cell cycle checkpoints are surveillance mechanisms that link the rate of cell cycle transitions to the timely and accurate completion of prior dependent events.
- Cells can arrest at cell cycle checkpoints temporarily to allow for (1) the repair of cellular damage; (2) the dissipation of an exogenous cellular stress signal; or (3) availability of essential growth factors, hormones, or nutrients.
- The major function of the p53 tumor suppressor protein is to induce cell cycle arrest, senescence, or death in response to cellular stress.
- Activation of the G_1, S, and G_2 phase checkpoints after DNA damage minimizes replication of damaged DNA templates or their segregation to daughter cells.
- Activation of the mitotic spindle checkpoint prevents defects in chromosome segregation and protects against aneuploidy.
- Disruption of cell cycle controls is a hallmark of all malignant cells. Disruption can manifest as alterations of growth factor signaling pathways, dysregulation of the core cell cycle machinery, and/or disruption of cell cycle checkpoint controls.
- Because cell cycle control is disrupted in virtually all tumor types, the cell cycle-related gene products that are mutated in tumors provide therapeutic targets that might preferentially affect tumor cells more than normal tissues.

INTRODUCTION

The majority of the cells in the adult body are arrested in a quiescent state, called the G_0 state. Most of these cells are terminally differentiated and never divide. However, specific populations retain the ability to proliferate throughout the adult life span, and this is essential for viability. For example, cells of the hematopoietic compartment and the gut have a high rate of turnover, and high rates of proliferation are therefore essential for the maintenance of these tissues. On average, about 2 trillion cell divisions occur in an adult human every 24 hours (about 25 million per second). The decision to proliferate or not is very tightly regulated. It is influenced by a variety of exogenous signals, including nutrients, mitogenic (e.g., epidermal growth factor and platelet-derived growth factor) and inhibitory (e.g., transforming growth factor-β) growth factors, and the interaction of the cell with its neighbors and with the underlying extracellular matrix. Each of these factors stimulates intracellular signaling pathways that can either promote or suppress proliferation. The cell integrates all of these signals, and if the balance is favorable, the cell will initiate the proliferation process. Anything that disrupts this balance can lead to either the reduction or expansion of a particular cell population. It is now clear that such changes are a hallmark of tumor cells. They carry mutations that impair signaling pathways that suppress proliferation and/or activate pathways that promote proliferation.

It is essential that proliferating cells copy their genomes and segregate them to the daughter cells with high fidelity. Over the past three decades, extensive effort has been placed on unraveling the basic molecular events that control this process. Studies in a variety of organisms have identified evolutionarily conserved machinery that controls eukaryotic cell cycle transitions through the action of key enzymes called cyclin-dependent kinases (CDKs). Eukaryotic cells have also evolved a series of surveillance pathways, termed *cell cycle checkpoints*, that monitor for potential problems during the cell cycle process. Human cells are continuously exposed to external agents (e.g., reactive chemicals and ultraviolet light) and to internal agents (e.g., by-products of normal intracellular metabolism, such as reactive oxygen intermediates) that can induce DNA damage. The cell cycle checkpoints detect DNA damage and activate cell cycle arrest and DNA repair mechanisms, thereby maintaining genomic integrity. Most, if not all, human tumor cells have mutations within key components of both the cell cycle machinery and checkpoint pathways. This has important clinical implications, as the presence of these defects can modulate cellular sensitivity to chemotherapeutic regimens that induce DNA damage. This chapter focuses on the