Introduction: Current Themes on Cell Cycle and Cancer

Xavier Graña

Genes & Cancer
3(11-12) 612-613
© The Author(s) 2013
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1947601913479021
http://ganc.sagepub.com

Keywords: CDK, CDC2, cyclins, retinoblastoma protein, checkpoints, phosphorylation, ubiquitination, stem cells, DNA replication, mitosis

Pioneering discoveries leading to our current understanding of the cell cycle date back more than 40 years with the identification of the maturation-promoting factor (MPF) in frog oocytes by Masui and Markert.¹ Subsequent studies took advantage of the power of yeast genetics and the development of more refined molecular biology techniques to identify and characterize cell cycle genes in the budding and fission yeasts in the Lee Hartwell and Paul Nurse laboratories, which resulted in the identification of *cdc2*, a gene required at the G1/S and G2/M transitions in fission yeast that was later found conserved from yeast to humans.²⁻⁴ Using marine urchin eggs and cellular and biochemical assays, Evans *et al.*⁵ identified cyclins as proteins whose expression changed abruptly during the cell cycle. Great efforts followed to demonstrate that CDC2 in association with a cyclin was the MPF.⁶ An explosion of discoveries led to our current understanding of the cell cycle in eukaryotes in which CDC2 is the founding member of the cyclin-dependent kinase (CDK) family. CDKs are activated by cyclins and certain phosphorylation events and negatively regulated by cyclin-dependent kinase inhibitors (CKIs) and other phosphorylation events.^{7,8}

A complex regulatory network of protein kinases, phosphatases, transcription factors, and ubiquitin-modifying enzymes ensures the precise activation and inactivation of CDKs at specific points in the cell cycle, triggering major transitions via phosphorylation of a

variety of substrates in all eukaryotes.⁹ CDKs are the engine that trigger the critical cell cycle processes of DNA replication and chromosome segregation, but also the downstream integrators of checkpoint signaling, thus allowing the cell cycle to halt in response to DNA damage, chromosome/spindle malfunctions, suboptimal growth conditions, and in metazoans, tissue-specific cues. Two major tumor suppressors, the retinoblastoma protein (pRB) and p53, are intimately integrated with this network.¹⁰ pRB (and related family members) suppresses growth by repressing the transcription of cell cycle genes and is a major substrate of CDKs that inactivate them in mid- to late G1.¹¹ p53 mediates checkpoint signals that halt the cell cycle by inhibiting CDKs.¹² Given the critical importance of the cyclin/CDK network for ensuring efficient progression through the cell cycle in metazoans, it is not surprising that cancer cells evolve to eliminate the checkpoints that ensure the fidelity of all these processes and to acquire the capacity to cycle independently of the tissue-specific cues that restrain proliferation to the needs of tissue cell renewal.

This monograph issue of *Genes and Cancer* includes reviews on recent advances in our knowledge of the cell cycle and its deregulation in cancer and is organized into 4 major themes that loosely coincide with major cell cycle transitions or phases: G1/S, S, G2/M, and a fourth section that focuses on mechanisms that operate throughout the cell cycle.

The first theme, “Cell Cycle Progression through G1 and the G1/S Transition,” includes 6 review articles. Greg Enders, from the Fox Chase Cancer Center at Temple University School of Medicine, discusses recent discoveries that suggest that interphase CDKs are essential for cell cycle progression, an idea that was accepted for many years following their discovery based on a variety of experimental evidence but was challenged later by the unexpected relative “mild” phenotypes in mice with the ablation of individual or combinations of interphase CDKs or cyclins. Frederick Dick and colleagues, from Western University in Ontario (Canada), thoroughly discuss the myriad of post-translational modifications in addition to CDK-dependent phosphorylation that modulate the function of the retinoblastoma tumor suppressor protein and how this connects pRB to several known pathways as well as others yet to be characterized. Jeanne Cook and colleagues, from the University of North Carolina at Chapel Hill, comprehensively review the ubiquitin ligases that regulate the expression of the key regulators of DNA replication during prereplication complex assembly and

Temple University School of Medicine, Philadelphia, PA, USA

Corresponding Author:

Xavier Graña, Fels Institute for Cancer Research and Molecular Biology and Department of Biochemistry, Temple University School of Medicine, 3307 North Broad Street, AHP Building, Room 308, Philadelphia, PA 19140, USA
(Email: xgrana@temple.edu)

through the S phase and the potential for these proteins as targets of anticancer therapies. Richard Pestell and colleagues, from the Kimmel Cancer Center at Thomas Jefferson University, discuss the role of alterations on the expression of cyclins in the cell cycle, cell migration, chromosome instability, and its association with cancer, with a major focus on alterations that affect the expression of cyclin D1. Premkumar Reddy and colleagues, from the Department of Oncological Sciences at Mount Sinai School of Medicine, discuss the role of CDK4, which is activated by mitogen-stimulated D-type cyclins, in the cell cycle, development, and cancer by reviewing numerous mouse models in which CDK4 activity has been manipulated in different contexts. They also consider the potential of therapeutically targeting this G1 CDK in cancer. Finally, Patrick Viatour, from the Center for Childhood Cancer Research at the Children's Hospital of Philadelphia, discusses the links between the cell cycle and self-renewal and how stem cells are uniquely sensitive to the disruption of components of the cell cycle machinery and how some of these factors link regulation of the cell cycle to differentiation.

The second theme, "Replication," is covered by a review from Hillary Collier and colleagues from the Department of Molecular Biology at Princeton University. This review focuses on DNA replication origins, with thorough consideration of the mechanisms utilized by different organisms from bacteria to metazoans and the relationship to transcription and chromatin structure as well as the potential implications for cancer.

The third theme, "From the G2/M Transition to Mitotic Exit," includes 3 reviews. Izabella Sumara, from the Institute of Genetics and Molecular and Cellular Biology in Illkirch (France), discusses the role of ubiquitination/

deubiquitination during the cell cycle with special emphasis in mitosis, in particular, ubiquitination events that are linked to protein degradation and often ensure cell cycle directionality but also ubiquitin modification events that are not linked to proteasome-mediated degradation. Thierry Lorca and Anna Castro, from Université Montpellier CNRS (France), discuss the role of the recently discovered Greatwall-PP2A/B55 network in counteracting cyclin B/CDK1 function during mitotic entry and exit. Marcos Malumbres, from the Centro Nacional de Investigaciones Oncológicas (CNIO) in Madrid (Spain), focuses on a mitotic protein, TPX2, a partner of the Aurora A kinase that is involved in the regulation of the mitotic spindle and is found overexpressed in human cancer. TPX2 deregulation may be associated with chromosome instability and aneuploidy.

The fourth theme is focused on "Mechanisms of Regulation that Operate through the Cell Cycle." Robert Fisher, from the Department of Structural and Chemical Biology at Mount Sinai School of Medicine, focuses on the role of the metazoan CDK-activating kinase (CAK), which is itself a CDK (CDK7), in the sequential activation of cell cycle and transcriptional CDKs. This thought-provoking review proposes a link between both processes through CDK7 and discusses the different mechanisms leading to T-loop phosphorylation of CDK2 and CDK1 that help explain sequential activation with their preferred cyclin partners and also proposes potential mechanisms for T-loop phosphorylation of CDK4/CDK6. To close, we discuss the role of trimeric forms of the PP2A holoenzyme that are implicated in the activation of the retinoblastoma family of pocket proteins in equilibrium with CDKs through

the cell cycle. Of note, some of these complexes are the same that counteract phosphorylation of CDK1 substrates during mitosis. We also discuss the tumor suppressor activities of PP2A and the potential implications of *PPP2R2A* disruption in a variety of cancers, as this gene encodes the B55 α regulatory subunit of a PP2A holoenzyme that targets pocket proteins and CDK1 substrates.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Masui Y, Markert CL. Cytoplasmic control of nuclear behavior during meiotic maturation of frog oocytes. *J Exp Zool*. 1971;177:129-45.
2. Hartwell LH, Mortimer RK, Culotti J, Culotti M. Genetic control of the cell division cycle in yeast, V: genetic analysis of *cdc* mutants. *Genetics*. 1973;74:267-86.
3. Beach D, Durkacz B, Nurse P. Functionally homologous cell cycle control genes in budding and fission yeast. *Nature*. 1982;300:706-9.
4. Lee MG, Nurse P. Complementation used to clone a human homologue of the fission yeast cell cycle control gene *cdc2*. *Nature*. 1987;327:31-5.
5. Evans T, Rosenthal ET, Youngblom J, Distel D, Hunt T. Cyclin: a protein specified by maternal mRNA in sea urchin eggs that is destroyed at each cleavage division. *Cell*. 1983;33:389-96.
6. Kirschner M. The cell cycle then and now. *Trends Biochem Sci*. 1982;17:281-5.
7. Morgan DO. Principles of CDK regulation. *Nature*. 1995;374:131-4.
8. Sherr CJ, Roberts JM. CDK inhibitors: positive and negative regulators of G1-phase progression. *Genes Dev*. 1999;13:1501-12.
9. Morgan DO. Cyclin-dependent kinases: engines, clocks, and microprocessors. *Ann Rev Cell Dev Biol*. 1997;13:261-91.
10. Hinds PW, Weinberg RA. Tumor suppressor genes. *Curr Opin Genet Dev*. 1994;4:135-41.
11. Weinberg RA. The retinoblastoma protein and cell cycle control. *Cell*. 1995;81:323-30.
12. Dash BC, El-Deiry WS. Cell cycle checkpoint control mechanisms that can be disrupted in cancer. *Methods Mol Biol*. 2004;280:99-161.