Cell Division

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Commentary

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APC/C – the master controller of origin licensing?

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Abstract

DNA replication must be tightly controlled to prevent initiation of a second round of replication until mitosis is complete. So far, components of the pre-replicative complex (Cdt1, Cdc6 and geminin) were considered key players in this regulation. In a new study, Machida and Dutta have shown that depletion of Emi1 caused cells to replicate their DNA more than once per cell cycle [1]. This effect was dependent on the ability of Emi1 to inhibit the APC/C. In addition to its role in regulating entry into mitosis, oscillation of APC/C activity regulates pre-RC formation: high APC/C activity in late M/G1 allows pre-RC formation and low APC/C activity in S/G2 prevents pre-RC formation for a second time thereby preventing rereplication. Each redundant pathway to prevent rereplication is dependent on regulating one of the pre-RC components, and all of the pathways are co-regulated by Emi1 through the APC/C. In this commentary we discuss how this new role of Emi1 adds to our understanding of the regulation of replication initiation. We also review the literature to analyze whether APC/C has a role in regulating endoreduplication (a normal state of polyploidy in some differentiated cells). Similarly a role of premature APC/C activation in genomic instability of tumors is discussed.

Background

DNA replication must be restricted to once per cell cycle and must be followed by mitosis to yield two cells each with the same amount of DNA. Hence replication is a tightly regulated process with many redundant pathways in place to prevent uncontrolled DNA synthesis (rereplication) and to ensure that each daughter cell receives a complete complement of chromosomes. To understand how replication is regulated we must first understand the factors that are involved in the process and how replication is controlled during the normal cell cycle.

The cell cycle describes the four stages of cell division. Specific enzymes called cyclin dependent kinases (cdks) along with their associated proteins (cyclins) regulate progression through the cell cycle. Cdk activity is tightly controlled by rapid synthesis and degradation of the associated cyclin. The first phase is G1 where the cells prepare to synthesize new DNA. Cyclin D/cdk4 activity increases early in G1 and this results in increased cyclin E/cdk2 activity late in G1 that promotes entry into the S phase. DNA synthesis is completed in the S phase and proper completion of this step is dependent on cyclin A/cdk2. In G2, cells prepare for division followed by M phase where the cells undergo mitosis. Cyclin A/cdk1 and cyclin B/cdk1 activity is required for G2 and M phase progression. Mitosis results in two daughter cells with a complete copy of the genetic material from the original cell.

The initiation of replication and its regulation is an area of active study and there are numerous excellent reviews on this subject [2-4]. Our current understanding of pre-RC