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Review

A roller coaster ride with the mitotic cyclins

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Abstract

Cyclins are discovered as proteins that accumulate progressively through interphase and disappear abruptly at mitosis during each cell cycle. In mammalian cells, cyclin A accumulates from late G_1 phase and is destroyed before metaphase, and cyclin B is destroyed slightly later at anaphase. The abundance of the mitotic cyclins is mainly regulated at the levels of transcription and proteolysis. Transcription is stimulated and repressed by several transcription factors, including B-MYB, E2F, FOXM1, and NF-Y. Elements in the promoter, including CCRE/CDE and CHR, are in part responsible for the cell cycle oscillation of transcription. Destruction of the mitotic cyclins is carried out by the ubiquitin ligases APC/C^{CDC20} and APC/C^{CDH1}. Central to our knowledge is the understanding of how APC/C is turned on from anaphase to early G_1 phase, and turned off from late G_1 till the spindle-assembly checkpoint is deactivated in metaphase. Reciprocal actions of cyclin-dependent kinases (CDKs) on APC/C, as well as on the SCF complexes ensure that the mitotic cyclins are destroyed only at the proper time.

Keywords: Anaphase-promoting complex; Cell cycle control; Cyclin; Cyclin-dependent kinases; Spindle-assembly checkpoint

Contents

1. Mitotic cyclins in mammalian cells

Cyclins are discovered as proteins that oscillate in synchrony with the cell cycle, accumulate progressively through interphase and disappear abruptly at mitosis [1–3]. These original "mitotic cyclins" were later recognized to be members of a family of proteins that function in mitosis as well as other phases of the cell cycle. Some cyclins also appear to have exclusively non-cell cycle functions. Cyclins associate with cyclin-dependent kinases (CDKs) and activate their kinase activity. One of the key moments in the cell cycle field is the discovery that the M-phase promoting factor (MPF) is composed of cyclin B and CDC2 (also called CDK1). MPF phosphorylates substrates that are critical for entry into mitosis, and destruction of the mitotic cyclins inactivates CDC2 and allows the cell to exit mitosis.

In mammalian cells, A- and B-type cyclins are synthesized and destroyed around the time of mitosis and are regarded as mitotic cyclins. Cyclin A also functions in S phase and its precise role in mitosis remains incompletely understood (reviewed in [4]). While cyclin B only activates CDC2, cyclin A can activate both CDC2 and CDK2. Another member of

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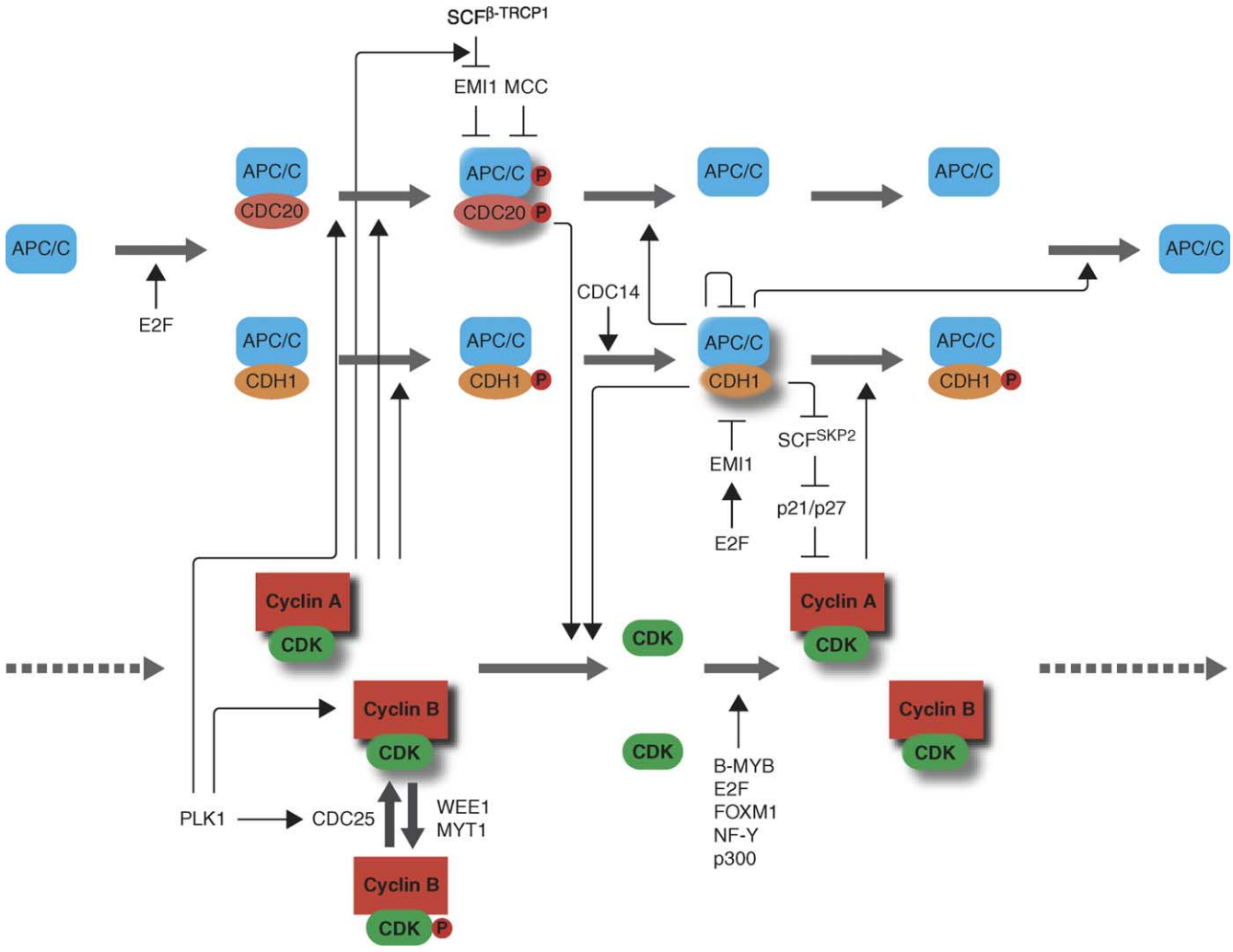

Fig. 1. Regulation of cyclin A and cyclin B in mammalian cells. See text for detail.

the family, cyclin F, is also produced and destroyed at the similar time as cyclin A. However, cyclin F does not have an essential mitotic function, and cyclin $F^{-/-}$ cells have reduced population-doubling time and a delay in cell cycle reentry from quiescence [5].

In mammalian cells, there are two A-type cyclins (A1 and A2) and three B-type cyclins (B1, B2, and B3). Cyclin A1 is only expressed during meiosis, in very early embryos, and in some tumor cells. The only essential function of cyclin A1 in mice appears to be in spermatogenesis [6]. In contrast, cyclin A2 is present in all proliferating somatic cells. Cyclin A2 is essential and disruption of its gene results in early embryonic lethality [7]. Cyclin B1 and cyclin B2 are co-expressed in the majority of dividing cells, but are differentially localized within the cell [8]. While cyclin B1 co-localizes with microtubules, cyclin B2 is associated with the Golgi apparatus. While mice lacking the *cyclin B1* gene die in utero, those lacking *cyclin B*2 develop normally and have no immediate phenotype (they seem to be less fertile and tend to be slightly smaller) [9]. Cyclin B3 degrades shortly after cyclin B1 but its expression is restricted to developing germ cells and in the adult testis [10].

One of the most crucial characteristics of the mitotic cyclins is their periodicity. Cyclin A starts to accumulate during late G_1 phase and continue through S phase and G_2 phase. Live cell imaging using cyclin A2-green fluorescent protein fusion proteins shows that human cyclin A2 begins to be degraded in early prometaphase and is completed at metaphase [11,12]. Cyclin B is both synthesized and destroyed slightly later than cyclin A [13–15]. The periodic expression of cyclin A and cyclin B is predominantly regulated at the levels of transcription and proteolysis. In this article, we summarize the current understanding of the synthesis and destruction of mitotic cyclins in mammalian cells (Fig. 1).

2. Transcription regulation of mitotic cyclins

Cyclin A mRNA accumulates and diminishes at the similar time as its protein, slightly ahead of cyclin B mRNA