DNA REPAIR 8 (2009) 6–18

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journal homepage: www.elsevier.com/locate/dnarepair

Invited Mini Review

Dual role of CDKs in DNA repair: To be, or not to be

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ARTICLE INFO

Article history:
Accepted 8 September 2008
Published on line 18 October 2008

Keywords:
Double-strand break repair
Homologous recombination
Cyclin-dependent kinase
Cell cycle
Repair regulation

ABSTRACT

The maintenance of genome integrity is essential for the regulation of cell proliferation and differentiation. DNA must be accurately duplicated and segregated to daughter cells at cell division, a process that is primarily regulated by cyclin-dependent kinases (CDKs). During cell growth, however, it is inevitable that DNA breaks will occur due to endogenous and exogenous stresses. Interestingly, there is increasing evidence that the catalytic activities of CDKs play critical roles in the DNA damage response, especially in the case of damage repaired by the homologous recombination (HR) pathway. In this review, we outline current knowledge of CDK regulation and its roles both in the unperturbed cell cycle and in DNA damage responses, and discuss the physiological roles of CDKs in HR repair.

Contents

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doi:10.1016/j.dnarep.2008.09.002

1. Introduction: CDK regulation and roles in the cell cycle

Regulated cell growth and differentiation are fundamental for development and homeostasis, and the basic molecular mechanisms of cell division are conserved among eukaryotes. These precisely regulated cell cycle events are primarily controlled by universal cell cycle 'engines', called the cyclin-dependent kinases (CDKs), first described in the 1980s.

1.1. *Regulation of CDKs*

In all eukaryotes, a variety of CDKs drive the initiation and progression of each successive phase of the cell cycle. The original member of the CDK family, now designated CDK1, was identified through genetic screens for yeast mutants with defects in the cell division cycle, designated Cdc2 (fission yeast) and Cdc28 (budding yeast) [1]. Intensive studies in the past 25 years have identified the human homologue of Cdc2 and additional members of this serine/threonine protein kinase family through various approaches including complementation of yeast mutants, biochemistry, and sequence homology [2–6]. Of the eleven human CDKs identified to date, four family members (CDKs 1, 2, 4 and 6) have well-characterised roles in cell cycle control, demonstrating periodical activation that is intricately regulated by multiple mechanisms (Fig. 1). First, although CDKs concentrations remain constant throughout the cell cycle, expression of their cognate protein partners, the cyclins, in many cases oscillates in a cell cycle-dependent manner, ensuring periodical activation of CDKs [7–9]. Second, activities of CDK-cyclin complexes are controlled by the opposing activities of Wee1/Myt1 kinases and Cdc25 phosphatases [10,11]. Wee1 and Myt1 inhibit CDK activity by phosphorylating the active site (Y15 and T14 in CDK2), while CDK activity is recovered by Cdc25-mediated de-phosphorylation. Such reversible CDK phosphorylation is essential for the regulation of cell cycle progression in both unperturbed and damaged cells. Finally, phosphorylation by the CDK-activating kinase (CAK) of a conserved threonine residue (T160 in CDK2) located on the activation T loop allows CDKs to be activated [12].

1.2. *Roles of CDKs in unperturbed cell cycle*

Activated CDKs phosphorylate numerous proteins that play primary roles in cell cycle events, such as DNA replication and cell division [13–15]. Temporal activation and CDK substrate specificity are critical for proper cell cycle progression. For example, initiation of DNA replication is precisely regulated through step-wise loading and activation of the replication machinery throughout G1 and the G1/S transition [16]. In G1, the origin recognition complex (ORC) is first loaded onto origins of replication, followed by association of Cdc6 and Cdt1, which in turn recruit the Mcm2–7 proteins, leading to the formation of inactive pre-replication complexes (pre-RCs). When CDK activity rises at the G1/S transition, pre-RCs are activated, partly by their association with additional replication factors such as Cdc45 and GINS [17]. Critically, CDK phosphorylation events not only stimulate DNA replication, but also block re-initiation of DNA replication. CDKs trigger disassembly of pre-RC complexes by phosphorylating Cdc6 and Cdt1 [18,19], thereby blocking *de novo* loading of pre-RC complexes during S and G2, and hence ensuring that there is only a single round of DNA replication per cell cycle.

In a similar fashion, the timing of mitotic entry and progression are carefully controlled by CDK1, which phosphorylates other mitotic kinases such as Polo-like kinase 1 (Plk1) and Aurora kinases, and multiple components of the mitotic apparatus required for nuclear envelope breakdown, spindle formation and chromosome condensation [13]. At the same time, CDK-dependent phosphorylation also blocks events in late mitosis such as chromosome segregation and cytokinesis. For example, CDK1 was recently shown to phosphorylate and stabilize securin, a negative regulator of separase, the protease that triggers sister-chromosome separation [20]. This mechanism plays a role in monitoring the readiness of all chromosomes for simultaneous segregation at the mitotic metaphase-anaphase transition, hence preventing premature cell division. Once all condensed chromosomes are aligned at the metaphase plate, CDK1 activity is down-regulated, partly through proteolysis of cyclins and partly through dephosphorylation by phosphatases, leading to the onset of chromosome segregation into daughter cells [21].

2. CDK regulation in damaged cells

CDKs ensure the orderly regulation of cell cycle events, which is essential for the maintenance of genome integrity, while the eukaryotic genome is constantly subjected to damaging assault by exogenous stresses such as radiation and chemotoxins, by endogenous pathological stress resulting from DNA replication and by by-products of cellular metabolism such as reactive oxygen species. These stresses cause various types of DNA damage such as inter- and intra-strand chemical cross-links, pyrimidine dimers, base alterations, and single- and double-strand DNA breaks [22]. Double-strand breaks (DSB) pose a particularly serious threat to genomic integrity as they can disrupt cellular processes such as transcription, replication and chromosome segregation, therefore leading to chromosome loss or anuploidy. To protect genomic information from such threats, DNA repair proteins are activated or transcriptionally induced, and are physically recruited to sites of DNA lesions, which are observed as distinct nuclear foci [23]. In the meantime, 'checkpoint' mechanisms allow proliferating cells to slow down cell cycle progression by down-regulation of CDK activities in order to provide time to repair broken DNA before entry into the next cell cycle phase [24].

In higher eukaryotes, the checkpoint responses are primarily mediated through two phosphatidylinositol 3-kinase-like kinases (PI3KKs) known as ATM (ataxia telangiectasia mutated) and ATR (ATM and Rad3-related), co-ordinating signalling pathways governing cell cycle delay and DNA repair [25–27]. ATM is first recruited to the damaged DNA in a manner that depends on direct interaction with the damage recognition MRN complex, which consists of Mre11 (meiotic recombination 11 homologue), a structural maintenance of chromosome (SMC) protein Rad50 and Nbs1 (Nijmegen breakage syndrome 1). ATM is then fully activated by auto- or