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Review

Cyclin-Dependent Kinases as Coregulators of Inflammatory Gene Expression

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Cyclin-dependent kinases (CDKs) exert a variety of functions through regulation of the cell cycle and gene expression, thus implicating them in diverse biological processes. Recent studies have deciphered the molecular mechanisms employed by nuclear CDKs to support the expression of inflammatory mediators. Induced transcription of many proinflammatory genes is increased during the G1 phase of the cell cycle in a CDK-dependent manner. This process involves the cytokine-induced recruitment of CDK6 to the nuclear chromatin fraction where it associates with transcription factors of the NF-κB, STAT, and AP-1 families. The ability of CDK6 to trigger the expression of VEGF-A and $p16^{INK4A}$ and to recruit the NF-κB subunit p65 to its target sites is largely independent of its kinase function. The involvement of CDKs in proinflammatory gene expression also allows therapeutic targeting of their functions to interfere with tumor-promoting inflammation or chronic inflammatory diseases.

Trends

CDKs in complex with various cyclins typically regulate the cell cycle or general RNA polymerase II functions during gene transcription.

Emerging data suggest that the CDKs 1, 2, 4, 6, 7, 9 and their regulators (cyclins, INK, and CIP/KIP proteins) have additional functions in regulating the inflammatory response.

CDK-dependent modulation of inflammatory genes in terminally differentiated immune cells occurs independently of the cell cycle.

Chromatin-associated CDKs interact with members of the NF-κB, STAT, and AP-1-families of inflammatory transcription factors through kinase-dependent and -independent mechanisms.

Therapeutic targeting of CDKs is predicted to affect cell migration, immune cell activation, neoangiogenesis, and inflammation, in addition to inhibiting cell proliferation.

CDKs and their Regulation

CDKs are multifunctional enzymes that can modify various protein substrates involved in the cell cycle. Human cells have 13 CDKs that interact with at least 29 cyclins or cyclin-related proteins, which allows the association of individual CDKs with a circumscribed subset of cyclins to create a large combinatorial repertoire of active CDK complexes [1]. As schematically shown in Figure 1, CDKs interacting with multiple cyclins (CDK1, 2, 4, 6) primarily regulate the cell cycle, whereas the CDKs activated by a single cyclin (CDK7, 9) are typically involved in the regulation of transcription. In the cell cycle, the activities of CDKs are positively regulated at several levels including the association with a specific cyclin and phosphorylation by a CDK-activating protein kinase (CAK) complex composed of CDK7, cyclin H, and MAT1 (menage à trois 1) [2,3] (Figure 1A). CDK activity is negatively regulated by two families of inhibitory proteins (Figure 1A). Members of the CIP (CDK interacting protein) and KIP (kinase inhibitory protein) family (composed of $p21^{CIP1}$, $p27^{KIP1}$, and $p57^{KIP2}$) bind to CDK/cyclin complexes and are able to inhibit CDK–cyclin once these complexes have already formed [4]. By contrast, INK4 (inhibitor of CDK4) family members (including $p16^{INK4A}$, $p15^{INK4B}$, $p18^{INK4C}$, and $p19^{INK4D}$) interact with monomeric CDK4 or CDK6, and thus prevent the activation by D-type cyclins or by CAK [5] (Figure 1A). Once assembled with the correct cyclin and phosphorylated at a threonine in the activation loop (also called the T-loop), the activated CDK4/6 phosphorylates its target proteins at serines or threonines such a retinoblastoma (RB) protein in the G1 phase of the cell cycle [6,7] (Figure 1B, upper left panel). Genetic and biochemical experiments identified CDK7 as the main CAK with the ability to phosphorylate the T-loops of all CDKs [8]. In addition, CDK7 is a subunit of the general transcription factor complex TFIIH (transcription factor II human). Within this complex CDK7 phosphorylates Ser5 and Ser7 contained in the C-terminal domain (CTD) of RNA polymerase (Pol) II and thus contributes to co-transcriptional capping, promoter-proximal

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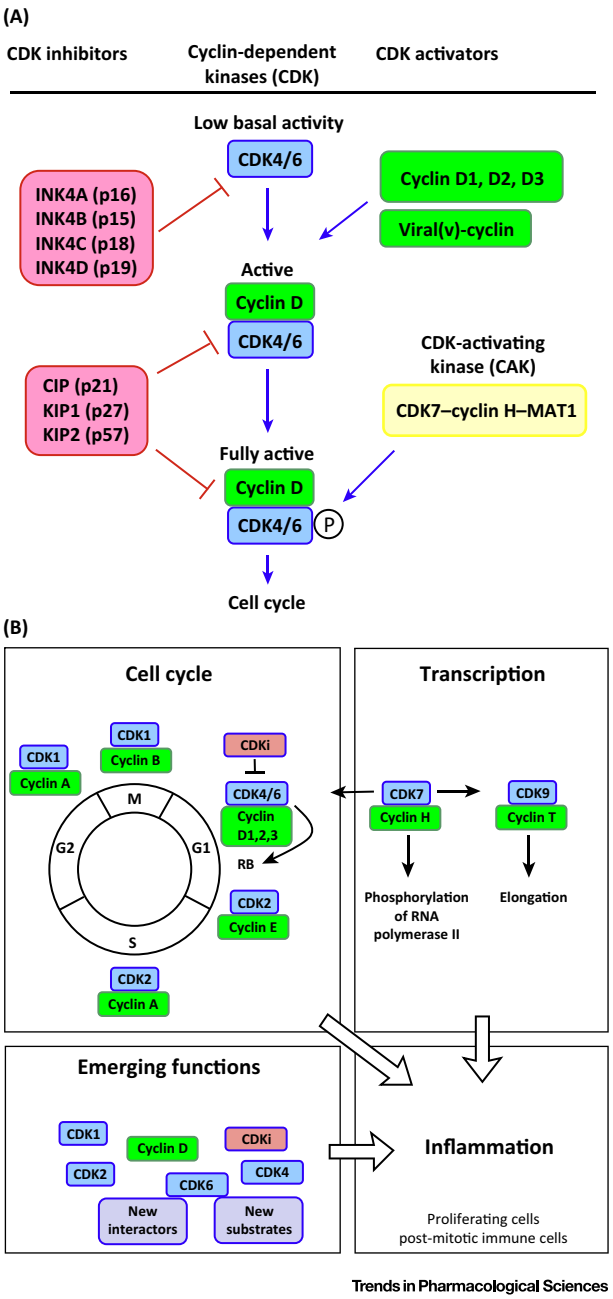

Figure 1. Regulation, Established, and Emerging Functions of CDK and Cyclin Families. (A) Regulation of the CDK4/6 family (blue) by cyclins (green), by the CAK complex (yellow) and by CDK inhibitory proteins (CDKi) of the CIP/KIP and INK4 families (red). Activating and inhibitory events that converge on the cell cycle are shown. (B) Established functions of specific cyclin/CDK complexes in the various cell cycle positions (upper left) and in basic transcriptional processes (upper right) are displayed. In addition, CDK-regulatory proteins and CDKs have a range of emerging functions that are likely to involve monomeric proteins and several newly identified CDK substrates and interactors (lower left). As outlined in this review all three processes contribute to regulation of inflammatory processes in both proliferating cells and in post-mitotic or terminally differentiated immune cells. Abbreviations: CAK, CDK-activating protein kinase; CDK, cyclin-dependent kinase; CIP, CDK interacting protein; INK4, inhibitor of CDK4; KIP, kinase inhibitory protein; MAT1, menage à trois 1; P, phosphorylation; RB, retinoblastoma.

pausing, and productive elongation [9,10]. CDK7 also phosphorylates and activates CDK9, which phosphorylates Ser2 in the RNA Pol II CTD, a modification that is essential for promoter-distal transcription elongation [11] (Figure 1B, upper right panel).

Investigations of mice lacking up to three CDKs identified the mitosis-regulating kinase CDK1 as the main essential component for the cell cycle, whereas ablation of other cell cycle regulators such as CDK2, CDK4, or CDK6 did not result in defective proliferation [12,13]. Mouse models and specific CDK inhibitors have revealed the involvement of CDKs in many different biological processes ranging from hematopoiesis, apoptosis, and senescence to DNA repair [6]. These