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MINI REVIEW

Cyclins: Roles in mitogenic signaling and oncogenic transformation

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Abstract
Cyclins are the regulatory subunits of kinases that control progress through the cell cycle. This review focuses on cyclins that are targets for extracellular signaling and frequently deregulated during oncogenesis, particularly cyclin D1. Receptor tyrosine kinases and adhesion molecules act through various effector pathways to modulate cyclin D1 abundance at multiple levels including transcription, translation and protein stability. In contrast, cyclin E-Cdk2 activity appears to be more commonly regulated by means other than regulation of cyclin E abundance. The importance of these pathways during oncogenesis is illustrated by the dependence of oncogenes such as Ras and Neu/ErbB2 on cyclin D1. Thus, understanding the roles of cyclins in growth factor and adhesion signaling is important for understanding the biology of both normal and neoplastic cells.

Keywords: *Cyclin D1, cyclin E, tyrosine kinase signaling, adhesion signaling, oncogenesis*

Introduction

The last 15 years has seen an explosion in the mechanistic understanding of cell cycle control, which has its origins in the identification of cyclins and cyclin-dependent kinases (CDKs) in experimental organisms as diverse as yeast, frogs and sea urchins. The timely activation of these kinases and consequent phosphorylation of specific substrates regulates progress through the different stages of cellular replication, in a basic mechanism that is conserved across evolution — a powerful illustration of the fundamental nature of the control of DNA replication and cell division. The multiple levels of external regulation necessary to ensure the correct spatial and temporal scheduling of cell proliferation in multicellular organisms are paralleled by multiple levels of control over the activity of the CDKs. This review focuses on cyclins, a key element of the regulation of CDK activity. In particular it concentrates on cyclins D1 and E, since these cyclins are under the most direct mitogenic control and are commonly deregulated during oncogenesis. Other G_1 cyclins, for example cyclins D2 and D3, are also overexpressed in human cancers, but much less commonly than cyclin D1 or cyclin E (Malumbres et al. 2001) and so will not be considered here in any detail.

Mechanisms of cell cycle control

Cyclins are the regulatory subunits of holoenzymes whose catalytic subunit is a CDK. Cyclins share a sequence motif termed the "cyclin box" that mediates binding to a similarly well-conserved region on the CDK (Morgan 1997). Members of this kinase family were originally characterised by virtue of their roles in cell cycle control, although more recently identified cyclin-CDK complexes have roles in transcriptional control (Garriga et al. 2004). In addition cyclin D1 can act as a transcriptional cofactor, a function which is CDK-independent (Coqueret 2002). As the name suggests, CDKs lack kinase activity in the absence of cyclin association and thus regulation of cyclin abundance is an important, but by no means the only, control mechanism for CDK activation (Morgan 1997).

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Progress through the cell cycle is accompanied by sequential accumulation of different cyclins that is correlated with the activation of specific cyclin-CDK complexes: cyclin E-Cdk2 at the G_1/S phase boundary, cyclin A-Cdk2 during S phase, cyclin A-Cdk1 (Cdc2) during G2 and cyclin B-Cdk1 during mitosis (Figure 1). The D-type cyclins (cyclins D1–D3) are less profoundly regulated during the cell cycle but are strongly mitogen-dependent. Consequently, the CDKs formed by association of D type cyclins and Cdk4 or Cdk6 can be viewed as "mitogen sensors", that act during G_1 phase to link signals from the extracellular environment to other CDKs that comprise the "core cell cycle machinery" (Sherr et al. 1999).

Several substrates for the different CDKs have been identified. A prevailing concept has been that each cyclin-CDK complex has a distinct substrate preference and that this specificity is a determinant in ordering cell cycle events. This is supported by several lines of evidence, for example the different spectra of cellular proteins phosphorylated by various recombinant cyclin-CDK complexes (Horton et al. 1997; Sarcevic et al. 1997) and the distinct consensus sequences for phosphorylation by cyclin D1-Cdk4 and cyclin E-Cdk2 or cyclin A-Cdk2 (Kitagawa et al. 1996). However, the ability of cyclin E and cyclin D2 "knocked-in" to the cyclin D1 locus to complement defects in mice lacking cyclin D1, and the ability of fibroblasts lacking all three D-type cyclins or both E-type cyclins to proliferate, argue for significant functional redundancy between the cyclins (Sherr et al. 2004). Thus, an alternative view is that the spatial and temporal control of cyclin expression is a major determinant of specificity (Murray 2004).

The best-understood CDK substrate is pRB, the product of the retinoblastoma susceptibility gene. The importance of pRB as a CDK substrate is illustrated by the observation that cyclin D1 is not required for G_1 phase progression in cells lacking pRB (Lukas et al. 1995). However, cyclin D1-associated CDKs are not the only pRB kinases; there are 16 possible consensus sites for CDK phosphorylation within pRB and the protein is progressively phosphorylated by different CDKs during cell cycle progression (Harbour et al. 2000). Phosphorylation of pRB by cyclin D-Cdk4 and/or cyclin D-Cdk6 early in G_1 phase displaces histone deacetylases from pRB and allows subsequent phosphorylation of pRB by cyclin E-Cdk2 and cyclin A-Cdk2 (Harbour et al. 1999). Phosphorylation by both sets of CDKs is necessary to completely overcome the growth inhibitory effects of pRB, release E2F transcription factors and allow initiation of DNA synthesis (Lundberg et al. 1998; Harbour et al. 1999). Recent data also implicate another CDK, cyclin C-Cdk3, in the phosphorylation of pRB during the transition from quiescence (G_0) to G_1 (Ren et al. 2004).

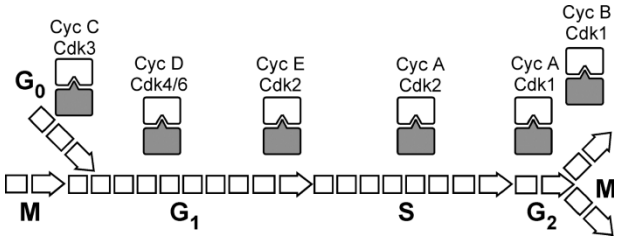

Figure 1. Cyclin-CDK complexes involved in cell cycle progression. The major cyclin-CDK complexes active in mammalian cells are illustrated. The different stages of the cell cycle are mitosis (M), quiescence (G_0), G_1, the DNA synthetic phase (S) and G_2. Cyc: cyclin.

In addition to regulation of cyclin abundance there exist several other levels of regulation for CDK activity including a network of regulatory kinases and phosphatases, and two families of endogenous small molecular weight CDK inhibitory proteins. The INK4 family of CDK inhibitors ($p15^{INK4B}$, $p16^{INK4A}$, $p18^{INK4C}$, $p19^{INK4D}$) specifically target Cdk4 and Cdk6 (Sherr and Roberts 1999). The Cip/Kip family inhibitors ($p21^{WAF1/Cip1}$, $p27^{Kip1}$, $p57^{Kip2}$) target a wider spectrum of CDKs. They profoundly inhibit the activity of cyclin E-Cdk2 and cyclin A-Cdk2, but also function as assembly factors for cyclin D-CDK complexes (LaBaer et al. 1997). Like the cyclins, these inhibitors are mitogen-responsive. For example, $p27^{Kip1}$ expression provides a "threshhold" that must be exceeded to allow CDK activation during mitogenic stimulation. One function of cyclin D1 appears to be sequestration of $p27^{Kip1}$: alterations in cyclin D1 abundance not only directly affect the activity of Cdk4 and Cdk6 but can indirectly influence the activation of cyclin E-Cdk2 by altering the availability of $p27^{Kip1}$ (Sherr and Roberts 1999).

Cyclin D1 regulation by receptor tyrosine kinase and adhesion signaling

Ras effectors: Mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways

It was apparent from some of the earliest studies of cyclin regulation in mammalian cells that many mitogenic signaling pathways converge on cyclin D1. For example, cyclin D1-neutralizing antibodies prevent DNA synthesis following stimulation by mitogens that activate either steroid hormone receptors, receptor tyrosine kinases or G-protein coupled receptors (Lukas et al. 1996). Subsequent studies have identified a number of levels at which intracellular signaling cascades, particularly those downstream of receptor tyrosine kinases, regulate cyclin D1 abundance or activity (see Figure 2). Receptor tyrosine kinase signaling through Ras to the Raf/MAPK kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway increases cyclin D1 transcription (Lavoie et al. 1996; Winston et al. 1996; Weber

et al. 1997). This depends on sustained ERK activation, at least in fibroblasts (Weber et al. 1997), and requires a binding site for ETS transcription factors in the cyclin D1 promoter (Albanese et al. 1995). In addition, MEK regulates cyclin D1-Cdk4 assembly, although induction of ectopic MEK is not sufficient for full activation of the resulting cyclin D1-Cdk4 complexes or S phase entry (Cheng et al. 1998).

Other Ras effectors, including PI3K and Ral, also activate cyclin D1 transcription (Gille et al. 1999), but this is not the only mechanism by which Ras effectors regulate cyclin D1 abundance. PI3K effects on translation of cyclin D1 mRNA have been documented (Muise-Helmericks et al. 1998; Koziczak et al. 2004). This is dependent on the mammalian target of rapamycin (mTOR) target S6 kinase 1 (S6K1) (Koziczak and Hynes 2004). However, an alternative target of mTOR, the repressor 4E-BP1, is also implicated in cyclin D1 translation. This protein binds the cap-binding protein eIF-4E, preventing the formation of the eIF-4F transcription initiation complex. mTOR-mediated phosphorylation of 4E-BP1 releases this inhibition (Richter et al. 2005). Although eIF-4E availability is rate-limiting for translation, increasing eIF-4E expression or activation over the level required for basal translation increases the translation of only a subset of mRNAs, including cyclin D1 (Rosenwald et al. 1993). Interestingly, this may be at least partially due an effect on nucleocytoplasmic transport of the cyclin D1 mRNA (Rousseau et al. 1996). Finally, there is evidence that the cyclin D1 mRNA also contains an mTOR-responsive internal ribosome entry site (IRES) that provides a means of cap-independent regulation of cyclin D1 translation (Shi et al. 2005). Protein kinase B (PKB)/Akt and mTOR regulate cell growth (i.e., increase in cell size) as well as cell proliferation (i.e., increase in cell number) and, at least in muscle cells, the former effect is mediated through S6K1 (Ohanna et al. 2005). In contrast, the dependence of cyclin D1 on S6K may appear to imply a S6K-mediated proliferative effect. However, in *Drosophila* the cyclin D-Cdk4 complex has roles in growth as well as proliferation (Frei 2004), raising the possibility that cyclin D1 may also regulate growth in mammalian cells.

PI3K activation of Akt leads to accumulation of cyclin D1 protein by a further post-transcriptional mechanism, in this case involving glycogen synthase kinase 3β (GSK-3β). The rate of cyclin D1 degradation is controlled by GSK-3β-dependent phosphorylation, and so inactivation of GSK-3β by Akt stabilises the cyclin D1 protein (Diehl et al. 1998). Wnt signaling also inactivates GSK-3β and thus leads to stabilization of the cyclin D1 protein (Rimerman et al. 2000) as well as stabilization of β-catenin to result in the activation of cyclin D1 transcription (Shtutman et al. 1999). This pathway of cyclin D1 induction downstream of Wnt co-operates with MEK to promote full activation of cyclin D1 and cell cycle progression (Rimerman et al. 2000). Similarly the Raf/MEK/ERK and PI3K/Akt pathways co-operate in the regulation of cyclin D1 after Ras activation (Gille and Downward 1999; Mirza et al. 2004).

Finally, while a predominantly G_1 phase role for cyclin D1 underlies much of the evidence reviewed above, there is also evidence that it may play a role in G_2 (Gabrielli et al. 1999). In continuously cycling cells, a Ras-dependent post-transcriptional effect leads to accumulation of cyclin D1 during G_2 and cyclin D1 is then Ras-independent during the subsequent G_1 phase, suggesting different control

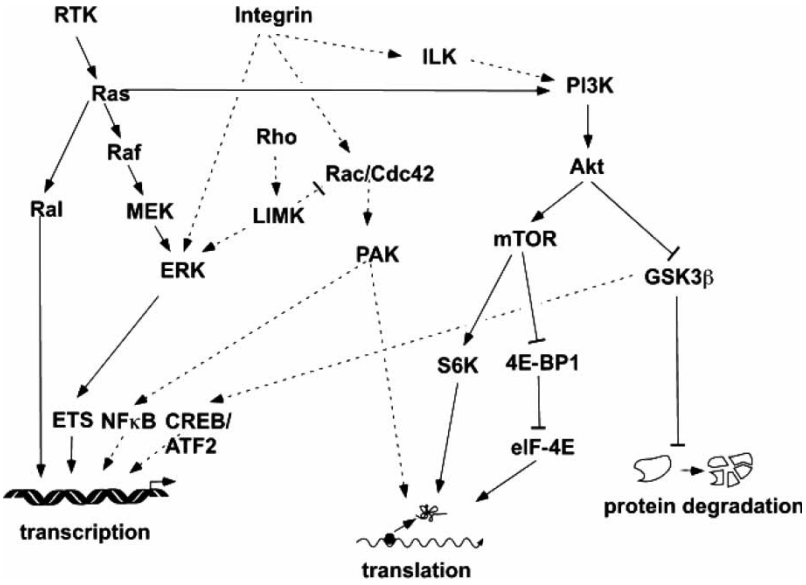

Figure 2. Regulation of cyclin D1 by receptor tyrosine kinase and integrin signaling. The major pathways by which cyclin D1 transcription, translation and protein stability are regulated downstream of receptor tyrosine kinases and integrins are illustrated. Dotted lines indicate integrin signaling.

mechanisms in continuously-cycling cells and cells stimulated to re-enter the cell cycle (Guo et al. 2002; Sherr and Roberts 2004). Although fibroblasts lacking all three D-type cyclins or both E-type cyclins can proliferate, they are defective in cell cycle re-entry upon mitogen stimulation and resistant to transformation by oncogenic Ras in conjunction with other "immortalizing" oncogenes (Sherr and Roberts 2004), adding further support to the idea that there are different control mechanisms for these distinct transitions and that the exit from quiescence (as distinct from transit through G_1 phase) may be of particular relevance to transformation.

Adhesion signaling. Proliferation requires both growth factor receptor activation and integrin-derived adhesion signals. The observation that cyclin D1 overexpression can induce anchorage-independent cell cycle progression in fibroblasts highlights the potential importance of this molecule in adhesion as well as mitogenesis (Resnitzky 1997). The regulation of cyclin D1 by integrin signaling is summarised in Figure 2, where the overlap between adhesion and receptor tyrosine kinase signaling is clear. A well-studied example is the sustained ERK activation that is necessary for increased cyclin D1 transcription, which requires both adhesion and growth factor signaling, at least in fibroblasts (Schwartz et al. 2001). In contrast, in epithelial cells there is evidence that adhesion-dependent induction of cyclin D1 can occur in the absence of growth factors, although this may depend on activation of the EGFR by integrin receptors (Bill et al. 2004) and thus again potentially reflects cross-talk between integrin and receptor tyrosine kinase signaling. The integrin-mediated ERK activation of cyclin D1 transcription occurs via an ETS binding site in the cyclin D1 promoter (Zhao et al. 2001). In addition, cyclin D1 transcription is also increased by the integrin-linked kinase (ILK), acting via the PI3K/Akt/GSK3β pathway (Radeva et al. 1997; D'Amico et al. 2000). This requires a CREB/ATF-2 site in the cyclin D1 promoter (D'Amico et al. 2000).

Members of the Rho family of GTPases — Rho, Rac and Cdc42 — regulate the actin cytoskeleton. They are necessary for cyclin D1 transcription and progress through G_1 phase (Olson et al. 1995; Westwick et al. 1997; Gille and Downward 1999; Roovers et al. 2003a) and play a significant role in linking adhesion signaling with cell cycle progression (Besson et al. 2004; Welsh 2004). The ability of Rac mutants to regulate cyclin D1 transcription in fibroblasts is closely correlated with their ability to bind the serine/threonine kinase PAK but not with their ability to activate the MAP kinase JNK/SAPK (Jun NH2-terminal kinase or stress-activated protein kinase) (Westwick et al. 1997). NFκB has been implicated as a downstream effector of Rac in this context (Joyce et al. 1999). In smooth muscle cells Rac induction of cyclin D1 transcription is dependent on the generation of reactive oxygen species by NADPH oxidase and this may also involve NFκB (Page et al. 1999). Integrin signaling also has been implicated in regulation of cyclin D1 translation in endothelial cells in a Rac-dependent, but MEK- and PI3K-independent, manner (Huang et al. 1998; Mettouchi et al. 2001).

In many cell types RhoA does not appear to signal directly to cyclin D1 but rather indirectly stimulates cyclin D1 gene expression by promoting the formation of actin stress fibers and hence sustained ERK activation (Besson et al. 2004). On the other hand, RhoA inhibits Rac-dependent cyclin D1 transcription (Welsh et al. 2001). This requires LIM kinase, but is independent of actin polymerisation (Roovers et al. 2003b). Thus Assoian and colleagues have proposed a model in which Rho coordinates the balance between cyclin D1 regulation by ERK and Rac and hence its dependence on the formation of stress fibers (Welsh et al. 2001; Besson et al. 2004). This also appears to coordinate the timing of cyclin D1 expression, since when Rac is not inhibited by Rho, cyclin D1 is prematurely expressed during early G_1 phase, rather than mid-G_1 phase (Welsh et al. 2001).

Cyclin E-Cdk2 regulation by receptor tyrosine kinase and adhesion signaling

In contrast with the extensive literature addressing the regulation of cyclin D1 during mitogenesis, relatively little attention has been paid to cyclin E, although its expression is also mitogen-dependent (Sherr and Roberts 2004). Regulation of CDK inhibitors has been more extensively studied and appears to be the major mechanism by which receptor tyrosine kinase and adhesion signaling regulate cyclin E-Cdk2 activity. In summary, Ras activation leads to downregulation of $p27^{Kip1}$ and $p21^{WAF1/Cip1}$ via both MAPK and PI3K (Malumbres et al. 1998; Liang et al. 2003), and Rho also targets these CDK inhibitors, which in turn negatively regulate Rho signaling (Besson et al. 2004). This is not, however, the exclusive means of growth factor regulation of cyclin E-Cdk2: other mechanisms with potential physiological relevance have been identified, for example the ability of ERK to regulate the activating phosphorylation of Cdk2 at Thr 160 (Lents et al. 2002), and the involvement of GSK3β in cyclin E protein stability (Welcker et al. 2003). In addition, recent evidence indicates that the Skp1-Cullin1 F-box protein-Fbw7 ubiquitin ligase, which targets Cdk2-bound cyclin E for degradation, is regulated by Ras (Minella et al. 2005).

Cyclins and oncogenesis

Evidence that cyclins are potential oncogenes comes from both experimental model systems and studies of human cancer. Both cyclin D1 and cyclin E1 are

deregulated in a substantial fraction of human cancers, including cancers of the breast, prostate, lung, gut, pancreas and head and neck, and in many cases this is associated with effects on prognosis (Malumbres and Barbacid 2001). Overexpression of cyclin D1 in the mammary gland leads to hyperplasia and eventually to carcinoma (Wang et al. 1994). In addition, overexpression in lymphocytes promotes lymphomagenesis, particularly when cyclin D1 and c-Myc are both overexpressed (Bodrug et al. 1994; Lovec et al. 1994). Similarly, cyclin E overexpression in mammary epithelium promotes tumor formation, but with low penetrance and long latency (Bortner et al. 1997), and can promote lymphomagenesis in cooperation with Ras (Karsunky et al. 1999). Thus cyclin D1 and cyclin E are oncogenic in mice, although weakly so, and it is likely that they co-operate with other oncogenes.

Given its role as a target of mitogenic signaling, it is not surprising that cyclin D1 is implicated in the oncogenic actions of Ras and Neu/ErbB2. In the mouse mammary gland, tumors induced by either oncogene display increased expression of cyclin D1 (Lee et al. 2000; Yu et al. 2001; Desai et al. 2002). Conversely, decreased cyclin D1 expression blocks the growth of tumors formed by mammary cells expressing activated Neu (Lee et al. 2000) and cyclin D1-null mice are resistant to tumor formation resulting from mammary-specific expression of Ras or Neu (Yu et al. 2001; Bowe et al. 2002). Interestingly, although cyclin D1 has also been implicated as a target of Wnt signaling, Wnt-stimulated oncogenesis was not impaired in cyclin D1-null mice (Yu et al. 2001). Overexpression of cyclin D1 in the skin does not lead to the development of tumors, but carcinogen-induced skin tumor formation characterised by a high frequency of Ha-Ras mutation is accompanied by an early increase in cyclin D1 expression (Robles et al. 1995; 1996). The development of these carcinogen-induced skin tumors is reduced in the absence of cyclin D1, as is skin tumor development following Ras expression (Robles et al. 1998). Thus the oncogenic actions of Ras and Neu are at least partially dependent on cyclin D1 in several tissues, although perhaps not all (Yu et al. 2001).

The observations that overexpression of $p15^{INK4b}$ and $p16^{INK4a}$, which target the cyclin D1-associated CDKs, can suppress Ras-mediated transformation *in vitro* (Serrano et al. 1995; Malumbres et al. 2000), that Ras co-operates with Cdk4 in the development of squamous cell carcinoma in human epidermis regenerated on mice (Lazarov et al. 2002), and that $p16^{INK4a}$ expression blocks ErbB2-induced mammary tumor formation in mice (Yang et al. 2004), all indicate that the dependence on cyclin D1 is likely to be mediated by the ability of cyclin D1 to increase CDK activity, either by direct activation of Cdk4 or by indirect activation of Cdk2 through sequestration of CDK inhibitors. Although the formation of mammary tumors after expression of activated Neu is impaired in cyclin D1-null mice, some tumors do develop and these are characterized by increased cyclin E expression (Bowe et al. 2002). Similarly, mice that have cyclin E "knocked-in" to the cyclin D1 locus develop Neu-induced mammary tumours at a rate similar to wild-type, indicating that cyclin E expression can compensate for the absence of cyclin D1 during oncogenesis. Again this is consistent with the idea that the requirement for cyclin D1 in mammary tumor development reflects a need for CDK activity, or at least proliferation.

The necessity for cyclin E in transformation has not been tested *in vivo*. However, in *in vitro* assays, fibroblasts lacking both cyclin E1 and E2 do not form foci in response to c-Myc or to Ras in combination with either Myc or dominant-negative p53. Although these fibroblasts display defects in cell cycle re-entry from quiescence, once proliferation is initiated it is only modestly impaired compared to controls with wild-type cyclin E, suggesting a specific requirement for cyclin E in oncogenic proliferation (Geng et al. 2003).

Conclusions

Perhaps the most striking aspect of the regulation of cyclins by extracellular signaling pathways is the diversity of means by which this is achieved, i.e., at the levels of transcription, translation, protein stability, complex formation and abundance of CDK inhibitors. The position of cyclins at the intersection of multiple pathways involved in oncogenesis has been one stimulus to the development of potential therapeutics targetting cyclins or CDK activity, some of which are now being tested in clinical trials (Senderowicz 2003). Recent evidence that CDK-independent functions of cyclin D1 likely contribute to its oncogenic actions (Lamb et al. 2003) and that CDK activity may not be as essential for cell cycle progression as first thought (Sherr and Roberts 2004) have led to questions over the likely efficacy of such approaches (Tetsu et al. 2003). However, while the cyclin D1- and cyclin E-activated CDKs are apparently not required for continuous proliferation in most somatic cells, they may play a more critical role in exit from quiescence and in the deregulated cell cycles of cancer cells (Sherr and Roberts 2004). The cyclins may also emerge as markers of therapeutic response: cyclin D1 expression confers resistance to the epidermal growth factor receptor-targeted therapy gefitinib in head and neck cancer cell lines (Kalish et al. 2004) and has been suggested as a marker of endocrine response in breast cancer (Butt et al. 2005). Although it is clear that cyclin function and regulation are rather more complex than was initially apparent, it is also clear that the ongoing further dissection of roles of these proteins is likely to have profound implications for understanding the cell biology of both normal and neoplastic cells.

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