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REVIEW

The elements of human cyclin D1 promoter and regulation involved

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Abstract Cyclin D1 is a cell cycle machine, a sensor of extracellular signals and plays an important role in G1-S phase progression. The human cyclin D1 promoter contains multiple transcription factor binding sites such as AP-1, NF- κB, E2F, Oct-1, and so on. The extracellular signals functions through the signal transduction pathways converging at the binding sites to active or inhibit the promoter activity and regulate the cell cycle progression. Different signal transduction pathways regulate the promoter at different time to get the correct cell cycle switch. Disorder regulation or special extracellular stimuli can result in cell cycle out of control through the promoter activity regulation. Epigenetic modifications such as DNA methylation and histone acetylation may involved in cyclin D1 transcriptional regulation.

Keywords Promoter · Transcription factor · Signal transduction pathway · Epigenetic regulation

Introduction

During the G1 phase, cells will response to the extracellular signals that influence cell division, growth, and differentiation. Cyclin D1 is thought to play pivotal roles in G1-S phase transition. Mistakes in G1 phase may lead to cell cycle out of control and cause tumorigenesis. Cyclin D1 is a sensor to integrate extracellular signals with the cell cycle machinery, with functions through CDK4/6 to trigger cell cycle progression. In recent years, accumulating evidence suggests cyclin D1 also convey cell cycle or CDK-independent functions, and cell can do without cyclin D1 (Coqueret 2002; Fu et al. 2004; Lamb et al. 2003; Pestell et al. 1999).

The cyclin D1 promoter sequence was studied and subcloned in several different laboratories (Albanese et al. 1995; Herber et al. 1994b; Motokura and Arnold 1993; Nagata et al. 2001). The promoter sequence, GenBank number Z29078 (Herber et al. 1994b), contains no obvious TATA box with TF (transcription factor) binding sites such as AP-1, SP-1, E2F, OCT-1, and so on. In this review, the structure of cyclin D1 promoter is discussed with such binding sites, and regulation from signal transduction pathway converging at the binding site.

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The elements of the cyclin D1 promoter

Cyclin D1 promoter popularly studied is 1,810 bp about with many *cis*-elements that can mediate signals activate or inactivate the promoter activity. From −1,309 (NFAT binding site) to −10 (Ets binding site), there are many regulatory elements reported. And if searching by computer program, there are some more elements that have not yet been studied. To compare the cyclin D1 promoter with rat and mouse, homologues region were found (Eto 2000), which can lead us to find new elements in human cyclin D1 promoter. The elements reviewed here only include the elements that have been studied (Fig. 1; Table 1).

AP1

AP1 site was identified in the promoter, which locates in −954 (Albanese et al. 1999). The site may be assigned TRE (12-O-tetradecanoylphorbol-13-acetate, TPA) response elements.

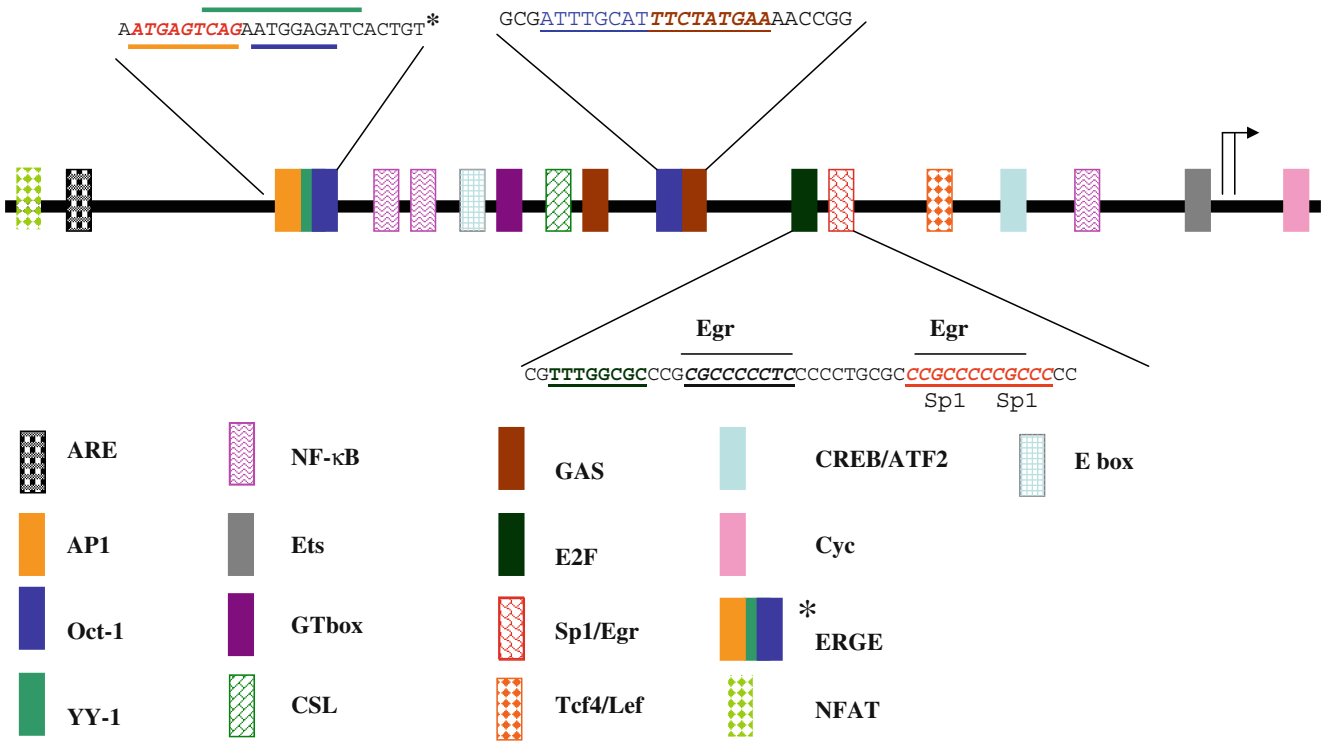

Fig. 1 Schematic representation of the elements of human cyclin D1 promoter. Elements of human cyclin D1 promoter are represented by *different colors*. Detail sequences of complex motifs such as ERGE (including AP-1, Oct-1, and YY-1) and Oct1-GAS are showed. Sequence of Egr-1 and Sp1 are also showed. Starting site of transcription is by *two arrows* due to the data of the referenced papers, and the sequences are showed in the manuscript

AP1 family protein, such as c-Fos, c-Jun, JunB, JunD, ATF, Fra-1, Fra-2, and so on, can bind at this site by forming homo- or heter-dimer (Fig. 1).

c-Jun (Albanese et al. 1995; Cicatiello et al. 2004; Mechta et al. 1997; Soh and Weinstein 2003) Fra-1 (Burch et al. 2004; Mechta et al. 1997) Fra-2 (Balmanno and Cook 1999) can activate cyclin D1 transcription. ATF3 (Allan et al. 2001) activate cyclin D1 promoter activity requiring cAMP response element-binding (CREB) site involved although it directly bind to AP-1 site. c-Fos may sometime

Table 1 Positions of TF elements in human cyclin D1 promoter

elements	location	reference
CREB/ATF2	−58	J Biol Chem, 1999 .274(11):7341
Lef/Tcf 4	−82	J Boil Chem, 2002 .277(48):45847
Sp-1	−113, −119	J Biol Chem, 1997 .272(52):33181
Egr	−137, −118	J Biol Chem, 1997 .272(52):33181
E2F	−148	Mol Cell Biol, 2000. 20(2): 672
GAS	−478, −144	Mol Cell Biol, 2003. 23(24): 8934–45
Oct_1	−252	Mol Cell Biol, 2003. 23(24): 8934–45
GT-boxA	−494	Mol Cell, 2003.11(6):1503
CSL	−525	Mol Cell Biol, 2001. 21(17): 5925
E-box	−588	Epigenetics, 2009.4(7):487–99
Ets	−779	Mol Biol Cell, 2001.12(12):4066
Oct_1	−941	Mol Cell Biol, 2004.24(16):7260
YY-1	−945	Mol Cell Biol, 2004.24(16):7260
AP-1	−952	Mol Cell Biol, 2004.24(16):7260
ERGE	−952	Mol Cell Biol, 2004.24(16):7260
NFAT	−1,309	J Biol Chem, 2009.284:36302-36311

Elements locations in human cyclin D1 promoter here are normalized to the paper (Motokura and Arnold 1993) and may be some different to the reference showed in the table

depress (Albanese et al. 1995) or activate (Brown et al. 1998; Cicatiello et al. 2004; Watanabe et al. 1996b) cyclin D1 promoter. JunB usually inhibits cyclin D1 promoter and can antagonized the c-Jun activation of cyclin D1 promoter (Shaulian and Karin 2001). A change of AP-1 composition toward an increase of JunB results in downregulation of cyclin D1 (Grosch et al. 2003). So generally c-Jun is an activator and JunB a repressor of cyclin D1 promoter. c-Fos is expressed rapidly and transiently (Balmanno and Cook 1999), so the inhibition effect by c-Fos overexpression (Albanese et al. 1995) probably cannot function in real cell cycle, except for c-Fos prolonged binding by some stimulation, e.g., oxidative stress (Burch et al. 2004).

Not only protein level but also the phosphorylated modification status is important to AP-1 proteins. c-Jun activation of cyclin D1 promoter requires phosphorylated on Ser63/73-Pro motifs (Wulf et al. 2001). Phosphorylation of JunB results in decreased JunB protein levels in mitotic and early G1 cells. In contrast, c-Jun levels remain constant with N-terminal phosphorylation. And the modifications of AP-1 proteins may regulate cyclin D1 transcription temporally to control cell cycle progression (Bakiri et al. 2000).

Some TFs in addition to Ap-1 family may regulate cyclin D1 promoter activity through AP-1 site directly (Roche et al. 2004) or indirectly, e.g., by protein interaction (Albanese et al. 1999), cooperation with other TF binding sites such as CREB (Watanabe et al. 1996a).

GAS

Among the STATs, only STAT3 and STAT5 can bring about the activation of cyclin D1 (Bromberg et al. 1999; Calo et al. 2003; Leslie et al. 2006).

Literatures showed that activated form of STAT3 was accompanied by increased expression levels of cyclin D1 (Bromberg et al. 1999; Kijima et al. 2002; Leslie et al. 2006; Masuda et al. 2001, 2002). And some paper showed that STAT3 can inhibit cyclin D1expression (Zhang et al. 2003). And during the liver regeneration after partial hepatectomy, the cyclin D1 induction was repressed, but STAT3 was unchanged in mice (Chen et al. 2004), which may suggest that modification of STAT3 is important to its activity. Data also showed cyclin D1 overexpression and STAT3 activation were, mutually exclusive events in MM (Quintanilla-Martinez et al. 2003).

But there was no evidence showing STAT3 can directly function through the cyclin D1 promoter, lacking data such as EMSA, ChIP and so on (Masuda et al. 2001, 2002). Moreover, cyclin D1 repression may due to CDKN1A or CDKN1B promoter induction. There are some evidences shows that STAT3 can active CDKN1B or CDKN1A promoter through PI3K pathway. Clearly, PI3K pathway can induce cyclin D1 promoter, and new evidences (Bienvenu et al. 2005) show that cyclin D1 is recruited to the CDKN1A promoter by a STAT3-NcoA complex leading to an inhibition of the p21waf1 gene (Bienvenu et al. 2005). In conclusion, in some context STAT3 and cyclin D1 balanced in cell cycle regulation but generally the relation between cyclin D1 and STAT3 may due to cell type and now is unclear.

Unlike STAT3, STAT5 can directly bind cyclin D1 promoter in which there are two STAT binding sites, one called GAS1 the other is GAS2 (Magne et al. 2003). The GAS1 site (distal) can bind stat5a/b which can activate cyclin D1 promoter (Brockman et al. 2002; Magne et al. 2003; Matsumura et al. 1999).The phosphorylated modification of STAT5b at Tyr679 induces STAT5b activation and then activate cyclin D1 promoter through interaction with other transcription factors, such as LEF1 and CREB/ATF2 (Kabotyanski and Rosen 2003). STAT5a lacks the Tyr679 site which can explain why only STAT5a/5b heterdimer or STAT5b/5b homodimer but not STAT5a/5a homodimer bind to the cyclin D1 promoter (Magne et al. 2003). Unlike GAS1, the GAS2 site, accurately composite Oct-GAS element, may be masked by Oct-1 protein which binding site overlap with GAS2. The binding of STAT5 to this site is required both GAS2 and OCT-1 element, with the interaction between STAT and PAU domain of Oct-1 (Magne et al. 2003).

E2F

The E2F binding sites in cyclin D1 promoter illustrate Fig. 1. Among five members of the E2F family, including E2F1, 2, 3, 4, and 5, only E2F1and E2F4 can bind this promoter (Watanabe et al. 1998). E2F transcription factors are bound to RB protein, and when RB is phosphalated by cyclin D1/CDK4, 6, E2Fs are released free. The free E2Fs then regulate their target genes promoting cell cycle progression.

Cyclin D1/CDK4, 6, RB and E2F cooperate together to enter cell cycle and progression in normal cell or to be transformed in tumor cell lines. Although cyclin D1 is upstream upon E2F protein during cell cycle, there are three feedbacks loop between cyclin D1 and E2F to facilitate the progression. E2F4 expresses at early G1 phase (Muller et al. 1997) which can activate cyclin D1 and results in more E2F4 protein level. This is a positive feedback loop, which occurs at early phase of cell cycle and let cell enter cell cycle quickly. There are also two other feedback loops, which respectively result in cell cycle arrest or progression depending cell types. E2F4 and E2F1 are functionally different which also express at different time in cell cycle (Muller et al. 1997). Contrast to E2F4, E2F1 expresses at late G1 phase (Muller et al. 1997). E2F1 regulates a set of genes that can let cell cycle progression. Depending different cell context, E2F1 can activate (Inoshita et al. 1999) or depress (Watanabe et al. 1998) cyclin D1

expression. High level of free E2F1 protein can induce proliferation then apoptosis (Knezevic and Brash 2004). Transgenetic mice expressing high level E2F1 also induce apoptosis (Pierce et al. 1998a). In this context, free E2F1 can depress cyclin D1, which formed a negative feedback loop to avoid apoptosis (Watanabe et al. 1998). The last feedback loop is that free E2F1 proteins can active cyclin D1 (Fan and Bertino 1997). The high level free E2F1 protein can activate another set of genes, e.g., FGFR which let cell cycle progression or transformed cells (Tashiro et al. 2003). The affinity of E2F1 to cyclin D1 promoter is higher than E2F4 (Lee et al. 2000). E2F1 has more potent activator activity than E2F4 (Pierce et al. 1998b). E2F-4 is located in nucleus from G0 until mid-G1 phase and mainly cytoplasmic in late G1, S, and G2 phases. In contrast, endogenous E2F-1 is absent from resting cells and is predominantly nuclear in late G1 and S (Muller et al. 1997). Due to the different affinity, at early stage E2F4 bounding that induce cell cycle entrance, and at late stage E2F1 take place of E2F4 results in cell cycle progression or transformation.

When depression of cyclin D1 promoter by E2F1, the SP1/2/3 is needed (Watanabe et al. 1998). Sp1 is inducible in early–mid-G1 phase (Nagata et al. 2001). In conclusion, E2F4 activate cyclin D1 promoter whereas E2F1 can activate or depress cyclin D1 promoter due to cell context.

NF-κB

NF-κB contributes to cell cycle progression, and one of its targets might be cyclin D1in T47D cell (Hinz et al. 1999). Dbl and Dbs regulated transcription from the cyclin D1 promoter in a NF-κB-dependent manner (Whitehead et al. 1999). Examination of the sequence from the human cyclin D1 promoter identified potential NF-κB-binding sites at positions −858, −749, and −39 that matched the NF-κB consensus binding sequence, GGG(G/A)NNYYCC (Guttridge et al. 1999). Different NF-κB complex members, p65 p50 and p52, can bind these sites (Guttridge et al. 1999; Westerheide et al. 2001). Although there are three NF-κB-binding sites, only the proximal site (−39) may be functional (Guo et al. 2009).

Generally NF-κB binding can induce cyclin D1 promoter(Joyce et al. 1999), whereas PKC delta depress cyclin D1 through NF-κB binding to −39 site (Page et al. 2002). Bcl-3, a co-activator with NF-κB p52 homodimers, was demonstrated to directly activate the cyclin D1 promoter through an NF-κB binding site (Westerheide et al. 2001), whereas p53 represses cyclin D1 transcription through this site under UV treatment downregulating of Bcl-3 (Rocha et al. 2003). Data also showed p53 can inhibit cyclin D1 promoter under heat shock (Guo et al. 2009). So stress stimulations may depress cyclin D1 through the proximal NF-κB binding site.

CREB/ATF2

The cAMP can inhibit or induce cell cycle progression and cyclin D1 expression. The CRE/ATF2 binding consensus site in cyclin D1 promoter locates at −57 (D'Amico et al. 2000; Lee et al. 1999; Musa et al. 1999; Watanabe et al. 1996a), which can bind CRE/ATF2 (D'Amico et al. 2000; Lee et al. 1999; McMahon et al. 1999; Musa et al. 1999), c-Jun (ATF-2/c-Jun heterodimers; Sabbah et al. 1999), CREM1 (Page et al. 2002), ATF1 (Schneider et al. 2002), and c-Fos (Brown et al. 1998). The effecter of Wnt signal transduction pathway, β-catenin/Tcf4, can also bind this site to induce cyclin D1 promoter (Pradeep et al. 2004). Galectin-3 (Lin et al. 2002) and G-17 (Pradeep et al. 2004) induces the cyclin D1 promoter also via the CREB site. Cyclosporine effective element overlaps the element and confers cyclosporine sensitivity to the cyclin D1 promoter (Schneider et al. 2002). PPAR gamma2 (Sharma et al. 2004), PKCdelta (Page et al. 2002) and p16INK4a (D'Amico et al. 2004) can inhibit cyclin D1 promoter through this site.

CREB Ser 133 phosphorylation is necessary for induction of cyclin D1 promoter through this site (D'Amico et al. 2000; Lee et al. 1999; Sharma et al. 2004), but the POU domain of oct-1 can potent its activation without Ser 133 phosphorylation by protein interaction (Boulon et al. 2002). But CREB Ser 133 phosphorylation may result in repression of cyclin D1 due to cell type (Musa et al. 1999).

TCF4

Nuclear β-catenin expression was correlated with cyclin D1 overexpression (Saito et al. 2001; Shtutman et al. 1999; Utsunomiya et al. 2001) with promoting malignant transformation by triggering cyclin D1 expression (Behrens 2000; Brabletz et al. 1999, 2000, Graham and Asthagiri 2004; Jung et al. 2004; Lepourcelet et al. 2004; Morin 1999; Muller-Tidow et al. 2004). TCF4 (Graham and Asthagiri 2004) and β-catenin (Shtutman et al. 1999) activate the cyclin D1 promote via the consensus TCF/LEF-binding sites (Grueneberg et al. 2003; Holnthoner et al. 2002; Tetsu and McCormick 1999). In addition to TCF4 mainly (Gotoh et al. 2003), LEF-1 (Grueneberg et al. 2003), HBP1 (Sampson et al. 2001), and UBF2 (Grueneberg et al. 2003) can also affect the cyclin D1 promoter activity by interaction with β-catenin or LEF-1.

β-catenin is a key component in the canonical Wnt pathway (D'Amico et al. 2000). Some molecules in addition to wnt, such as IKKα (Albanese et al. 2003), PTEN (Persad et al. 2001b), and SOX17 (Lange et al. 2009) can also regulate it. In addition to Wnt pathway, PI3k signal transduction pathway (Albanese et al. 2003; D'Amico et al. 2000), ILK (D'Amico et al. 2000; Persad et al. 2001b), RA (Shah et al. 2002), caveolin-1 (Hulit et al. 2000) can also

regulate cyclin D1 promoter activity via consensus this site in cyclin D1 promoter, and CREB site (Pradeep et al. 2004) may be needed.

E box

There is an E box element at −558 in human cyclin D1 promoter (Eto 2000; Magne et al. 2003; Zhang et al. 2002). The E box can bind Myc or other transcription factor, so some paper may assigned it c-myc element. Myc proteins bind to cyclin D1 promoter to inhibit its activity (Chien et al. 2008; Gonzalez-Mariscal et al. 2009; Philipp et al. 1994), probably inducing DNA methylation (Hervouet et al. 2009). The element may activate cyclin D1 promoter by different protein interaction with myc, e.g., Max (Yang et al. 2009).

Ets

In the proximal region of cyclin D1 promoter, an Ets (c-Ets2) site was first identified in 1995 (Albanese et al. 1995). There several putative Ets binding site in cyclin D1 promoter. Tetsu and McCormick (1999) demonstrated four other Ets sites which they named Ets A B C D, but only the B box is mediated by P21RAS. Zhao et al. (2001) demonstrated that the EtsB binding site mediated cyclin D1 promoter regulation by FAK. The proximal box can mediated PKC delta activity (Page et al. 2002), and RAS induced MAPK signal transduction (Albanese et al. 1995).

CSL

Notch, an evolution-conserved membrane crossed-signal molecular (for review, see Artavanis-Tsakonas et al. 1999) encoding a family of transmembrane proteins that are involved in many cellular processes such as differentiation, proliferation, and apoptosis, can activated cyclin D1 promoter transcription through a CSL site (Jeffries et al. 2002; Ronchini and Capobianco 2001; Stahl et al. 2006).

GT box

There are four GT box in cyclin D1 promoter but only the GT box A was active which was responsible for the inhibition effect of KLF8 to cyclin D1 promoter (Zhao et al. 2003).

Egr-1

In cyclin D1 promoter,Egr-1 site which overlaps two sp1 sites, can mediate TGFβ (Yan et al. 1997) and Ang II (Guillemot et al. 2001)-induced cyclin D1 upregulation. But unexpectedly the Egr-1 binding activity to the cyclin D1 promoter is not influenced by SP1 binding (Yan et al. 1997).

Sp1

The transcription factor SP1 is a DNA-binding protein which interacts with a variety of gene promoters containing GC-box elements. Among many possible SP1 sites, the site studied in the promoter overlaps with Egr-1. Induction of the cyclin D1 promoter activity in the early to mid G 1 phase is via the SP1 sites by the Ras-dependent pathway (Nagata et al. 2001). NeuT can induce cyclin D1 promoter by Sp1/3 binding in cooperation with E2F site (Lee et al. 2000). In PC12 cells NGF can induce neurite outgrowth and cyclin D1 transcription via Sp1 and NF-κB binding site in the proximal region of the cyclin D1 promoter (Marampon et al. 2008).

CycY

The motif is SP1-like but bind basic transcription element binding factor (BTEB) whose molecular weight is smaller than SP1 (Hsiang and Straus 2002).But binding BTEB on CycY site is not responsible for cyclopentenon (Hsiang and Straus 2002).

ARE

p19ARF repressed cyclin D1 through a novel distal *cis*-element ARE at −1137, which bound p53 revealed by chromatin-immunoprecipitation assays (D'Amico et al. 2004). P53 can also repress cyclin D1 promoter in −39 NF-κB site and HADC1 may involved (Guo et al. 2009; Rocha et al. 2003).

Complex motif

Complex motif here means that two elements in a promoter are very close, sometimes joined together. In this promoter, e.g., E2F and sp1, stat and oct-1 are close to form complex motifs. More often, the proteins that bound to complex motif could interact with each other. So we can deduce that proteins which can interact with each other may result in DNA sequence rearrangement. The protein and DNA sequence can co-evolve.

Starting site

Different groups studied the transcription star site with different methods (Herber et al. 1994a; Hsiang and Straus 2002; Motokura and Arnold 1993; Philipp et al. 1994). Among these, CCTCCAGAGGGCTGT (Motokura and Arnold 1993) and CCTCCAGAGGGCTGT (Hsiang and Straus 2002; transcription star site is underlined) were prevalently accepted. In this review, elements positions were normalized to CCTCCAGAGGGCTGT (Motokura and Arnold 1993).

Signal transduction pathway

There are mainly three signal transduction pathways involved in cyclin D1 promoter regulation, which are MAPK, PI3K/Akt, and Wnt. Others such as ER, NF-κB, JAK/STAT, Rac1/NADPH oxidase are also involved. Here, we discuss the main three pathways: MAPK, PI3K/Akt and Wnt including its molecules, response elements and cross-talk points (Fig. 2).

ERK1/2 cascade can activted cyclin D1 promoter activity. Raf/Mek/Erk pathway usually activates cyclin D1 promoter (Chu et al. 2005; Greulich and Erikson 1998; Page et al. 1999a, b; Ramakrishnan et al. 1998; Watanabe et al. 1996a, b; Weber et al. 1997a, b). There are two phases of ERK activation, of which the second sustained phase is required for activation of cyclin D1 promoter (Fassett et al. 2003; Talarmin et al. 1999; Treinies et al. 1999; Weber et al. 1997b). But the prolonged ERK activation results in downregulation cyclin D1 due to inhibition of CREB activity, including its DNA binding ability and Ser-133 phosphorylation (Wang et al. 2003), or due to ERK nuclear location (Burch et al. 2004; Clark et al. 2004). P38 usually inhibits (Catalano et al. 2004; Ellinger-Ziegelbauer et al. 1999; Kintscher et al. 2003; Lavoie et al. 1996; Lee et al. 1999; Page et al. 2001; Pruitt et al. 2002; Todd et al. 2004; Westwick et al. 1998) and sometimes activated (Klein et al. 2003; Lee et al. 2000, 1999; Recio and Merlino 2002) cyclin D1.SV 40 small antigen can induce cyclin D1 promoter by ERK and SAPK pathway (Watanabe et al. 1996a). JNK can activate cyclin D1 promoter via activating c-jun (Oktay et al. 1999; Wulf et al. 2001) and ATF2, which can by binding CREB/ATF2 site (Lee et al. 1999). But some literatures reported JNK also inhibited cyclin D1 promoter (Grosch et al. 2003) or had no function on cyclin D1 expression in bovine tracheal myocytes (Page et al. 1999a).

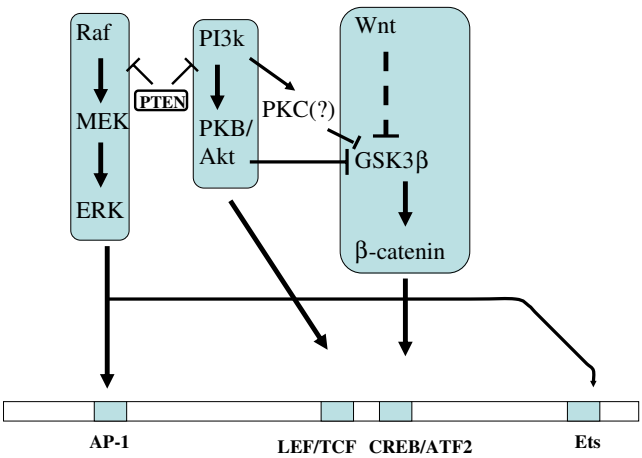

Fig. 2 The main three signal transduction pathways on human cyclin D1 promoter. Three pathways are MAPK, PI3k/Akt, and Wnt. MAPK pathways regulate cyclin D1 promoter via AP-1 and Ets elements. Elements such as LEF/TCF and CRE are responsible for PI3k/Akt and Wnt pathways and GSK3β is their cross-talk point. PETN can cross-talk between MAPK and PI3k/Akt pathway

ERK pathway induces cyclin D1 promoter by Ets or AP-1 (Chu et al. 2005) elements in cyclin D1 promoter (Albanese et al. 1995; Chu et al. 2005; Guillemot et al. 2001). V-src activation of cyclin D1 involved the ERK, p38, and JNK via CREB site (Lee et al. 1999), but in CCL39 cells, ERK5 but not the ERK1/2 cascade regulate cyclin D1 promoter via this site (Mulloy et al. 2003).

The Wnt signaling pathway is conserved in various organisms from worms to mammals, and plays important roles in development, cellular proliferation, and differentiation. Wnt stabilizes cytoplasmic β-catenin and then β-catenin is translocated into the nucleus where it stimulates the expression of genes including cyclin D1 (Kikuchi 2000; Shtutman et al. 1999; Tetsu and McCormick 1999). PI3k/Akt signal transduction pathway can inhibit GSK3β and then promote β-catenin to activate cyclin D1 promoter via the TCF site (Albanese et al. 2003). PI3k/Akt signal transduction pathway can also activate cyclin D1 promoter by modulating CREB via its binding site. But this may be weaker than that by inhibition of GSK3β (Xie et al. 2003). ILK and PDK1 can activate Akt by phasphation at different amino acid site, ser-473 and ser-308, respectively (Persad et al. 2001a), which all take part in Akt activation which consequently then inhibits GSK3β at ser-9 (Troussard et al. 2003). In some cell type, PKC but not Akt can inhibit GS3Kβ (Xie et al. 2003). Rac1 which can form positive regulation loop with PI3k (Welch et al. 2003), can activate cyclin D1 by NF-κB (Joyce et al. 1999) and CREB site (Bauerfeld et al. 2001; Joyce et al. 1999; Page et al. 2000) independent of ERK (Page et al. 1999b, 2000). Wnt pathway regulation whereby activation of Rac1 amplifies the signaling activity of stabilized/mutated β-catenin by promoting its accumulation in the nucleus, and synergizing with β-catenin to augment TCF/LEF-dependent gene transcription (Esufali and Bapat 2004). PI3k/Akt signal transduction pathway plays important role in regulation of cyclin D1 promoter. The pathway may induce cyclin D1 by CREB site in the promoter and can modulate GSK3β to activate β-catenin, which can induce cyclin D1. There are many interlinks between PI3k and wnt pathway in regulation of cyclin D1 promoter.

It is usually thought that MAPK, unlike wnt, distinct from PI3k signal transduction pathway (Page et al. 2000), but there are still many cross-talks between them. The ERK pathway modulated AKT phosphorylation by acting on the PTEN levels (Marino et al. 2003). Persad et al. (2001b) define a pathway that ILK and GSK-3 can regulate β-catenin stability, nuclear β-catenin expression, and its transcriptional activity. Wnt-transactivated ErbB1 was responsible for MAPK activation and the increased levels

of cyclin D1 present in the Wnt-expressing HC11 cells (Civenni et al. 2003). TGF-β1 also first decreases and later potentiates the levels of EGF-activated MEK1/MAPK and PKB, which results in initially suppresses EGF-induced cyclin D1 expression then later releases the inhibition (Yan et al. 2000) implying there are other cross-talks between MAPK and PI3k/Akt.

Taken together, there are cross-talks between Wnt and PI3k usually converging at GSK3β. MAPK pathway is generally distinct from PI3k, but they can cross-talk, e.g., by PTEN (Marino et al. 2003; Weng et al. 2001), TGF-β1 (Yan et al. 2000), PAK (Nheu et al. 2004), or others. PTEN is also involved in the regulation of nuclear β-catenin accumulation and TCF transcriptional activation in an APC-independent manner (Persad et al. 2001b). Sometimes in the mammary gland Wnt pathway can activate cyclin D1 by MAPK activation (Civenni et al. 2003).

The temporal expression of cyclin D1

Cell cycle progression requires different signal molecules function at the right time. The stimulation from growth factor is temporal, biphasic (Jones and Kazlauskas 2001). So what pathway function at what time is critical for cell cycle progression. Rac/Cdc42 signaling induces cyclin D1 expression in an early G1 phase. In the mid-G1 phase, cyclin D1 is induced by sustained ERK, which can be promoted by Rho kinase. At the same time, Rho kinase suppresses Rac/Cdc42 activity (Roovers and Assoian 2003; Roovers et al. 2003; Welsh et al. 2001). MKP, as an inhibitor of ERK, can form a feedback loop to a flexibly balanced ERK activity (Bennett and Tonks 1997; Bhalla et al. 2002; Ryser et al. 2004). MKP overexpression can result in downregulation of cyclin D1 (Kawanaka et al. 2001; Lavoie et al. 1996; Qin et al. 2005). In the later stages of G1, PI3k pathways instead of ERK to sustain cyclin D1 expression to perform S phase entry (Gille and Downward 1999; Marino et al. 2003). Akt/PKB, an important downstream of PI3k, is expressed in late G1phase (Gille and Downward 1999; Paramio et al. 1999), but it only influences partly cyclin D1 expression (Gille and Downward 1999). So there may be multiple signal molecules involved.

Epigenetic regulation of the cyclin D1 transcription

Epigenetic regulation means a heritable alteration in gene expression without the primary DNA sequence changing. The major mechanisms involved in epigenetic changes are modification of DNA and histone protein such as DNA methylation at cytosine bases and histone acetylation.

Epigenetic modification sites involved in cyclin D1 transcriptional regulation include (1) GC-rich Sp1/CRE binding site, (2) remote upstream region mainly in chromosome translocation, a common cause of blood tumor, (3) 1 kb upstream including E-box element, and (4) other DNA methylation sites which have not been studied. Actually, function of DNA methylation and histone modification are commonly studied together.

DNA methylation at Sp1/CRE binding sites of rat cyclin D1 promoter may be essential for keeping a number of the stromal cells in the basal layer live (Kitazawa et al. 1999). In hamster cell, using human cyclin D1 promoter, data showed that DNA methylation was found at Sp1/CRE binding sites (Hilton et al. 2005). However, the epigenetic modification including DNA methylation at cytosine bases and H3/H4 acetylation at Sp1/CRE binding sites may not be essential for transcriptional regulation of cyclin D1 (Krieger et al. 2005). Chromosome translocation, a common cause of blood tumor, is thought to transcriptional regulation of cyclin D1. Data showed that such epigenetic modifications mainly were found in the translocation region, distal upstream region of cyclin D1 promoter (120 kb from the transcriptional start site; Liu et al. 2004) and demethylation may due to CTCF and NPM (Liu et al. 2008a). Different group found the DNA methylation or histone acetylation in this region from different blood tumor including MCL, MM, and NHL and so on. Although the epigenetic modification may be essential in gene transcriptional regulation, it was thought that the epigenetic modification have no effect on cyclin D1 transcription. No DNA methylation was found in cyclin D1 promoter by genomewide methylation analysis in MCL patients (Leshchenko et al. 2010). The endogenous cyclin D1 promoter may be inaccessible to the transcription factor and cyclin D1 transcription may be control through other different manner. Actually the MYEOV gene which located approach to cyclin D1 was transregulated by this epigenetic modification (Janssen et al. 2002), which showed that epigenetic regulation may need a proper transcriptional status. Interestingly, in some MM and MCL samples that did not express cyclin D1, the cyclin D1 promoter was hypomethylated and hyperacetylated, which suggested that DNA methylation in the promoter may be related to malignant phase rather than to cyclin D1 regulation (Liu et al. 2004). And this agreed with the data in NHL research, in which the DNA methylation was identified as a tumor maker, although it is not involved in cyclin D1 transcription (Shi et al. 2007), which showed that the region was proven to be methylated. Genes other than cyclin D1 may be regulated by DNA methylation which can then regulated cylcin D1 including CDKN2A (Vonlanthen et al. 1998; Kawauchi et al. 2004; Takahira et al. 2004; Hutter et al. 2006; Liu et al. 2008b; Matsuda 2008; Takahira et al. 2004; Kawauchi et al. 2004; Hashiguchi et al. 2001; Hutter et al. 2006; Dominguez et al. 2002), wnt (Fox et al. 2008; Martin et al. 2009), and miRNA (Ilnytskyy et al. 2008). Data from

blood tumor, epigenetic modification in 1 kb region upstream from transcription start site may not affect cyclin D1 transcription (Liu et al. 2004). Although data from blood tumor cell mainly showed that epigenetic modification may not involved in cyclin D1 transcription, in glioma cells Hhervouet et al. (2009) showed a DNA methylation mechanism in depression of cyclin D1 transcription via E-box, a site-specific DNA methylation site in the 1 kb upstream region of cyclin D1.And different from blood tumor research which showed treatment of TSA or 5-Aza had no effect on cyclin D1 transcription (Krieger et al. 2005), data showed that the epigenetic regent can regulate its transcription or translation in glioma cell,H1299 cell, follicular lymphoma (also blood tumor) cell and MCF-7 cell (Alao 2007; Alao et al. 2006a, b; Bennett et al. 2009; Hervouet et al. 2009; Rocha et al. 2003). Data from HCC (primary liver cancer) showed DNA methylation in cyclin D1 promoter (Matsuda 2008) and in lung cancer, DNA methylation of CDKN2A promoter in regulation of cyclin D1 may be different (Zhou et al. 2001). So epigenetic regulation may be different due to cell types. Other than histone acetylation, histone methylation of H3k9 may inhibit human (Krieger et al. 2005) and mouse (Shirato et al. 2009) cyclin D1 transcription, and this may function in development (Ait-Si-Ali et al. 2004). Considering CpG islands identifying, other sites may be studied to reveal the epigenetic regulation mechanism involved in cyclin D1 for example there are many other CpG inlands (Krieger et al. 2005) except for the region mentioned above.

In conclusion, epigenetic modification (DNA methylation and histone modification) involved in cyclin D1 transcriptional regulation may be cell type-specific. In most blood tumor, cyclin D1 transcription is not due to DNA or histone modification, but this was not the barrier for the DNA methylation to be used as a putative tumor marker. Other gene (especially CDKN2A) may be regulated by epigenetic modification. There may be other epigenetic modification which can be studied to provide insight into a new mechanism of epigenetic transcriptional regulation of cyclin D1, for there are other CpG islands not studied yet.

Conclusion

Cell cycle control is complex, in which cyclin D1 transcription regulation may be important. But firstly, cell cycle control is not only in transcription level but also in post-transcriptionally regulated manner, e.g., protein degradation, modification, which all play an important role in cell cycle control. For example, GSK3β can also increases cyclin D1 protein degradation (Hamelers et al. 2002; Jirmanova et al. 2002; Kim et al. 2002; Zou et al. 2004), and cyclin D1 mRNA half-life becomes shorter when serum is removed (Guo et al. 2005). And secondly, much study got from synchronized cell by serum deprivation, which cannot reflect the real cycle. In actively cycling cells, cyclin D1 may be induced to high levels in G2 phase, and the expression levels of cyclin D1 in G2 phase determine the fate of the next cell cycle (Guo et al. 2005; Stacey 2003). Thirdly, some cell can proliferfy and organ developed without cyclin D1 (Kozar et al. 2004; Malumbres et al. 2004). Taken together, the regulation of cyclin D1 promoter is important in cell cycle control, but it is not all.

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