REVIEW

Atypical cyclins: the extended family portrait

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Abstract

Regulation of cell division is orchestrated by cyclins, which bind and activate their catalytic workmates, the cyclin-dependent kinases (CDKs). Cyclins have been traditionally defined by an oscillating (cyclic) pattern of expression and by the presence of a characteristic "cyclin box" that determines binding to the CDKs. Noteworthy, the Human Genome Sequence Project unveiled the existence of several other proteins containing the "cyclin box" domain. These potential "cyclins" have been named new, orphan or atypical, creating a conundrum in cyclins nomenclature. Moreover, although many years have passed after their discovery, the scarcity of information regarding these possible members of the family has hampered the establishment of criteria for systematization. Here, we discuss the criteria that define cyclins and we propose a classification and nomenclature update based on structural features, interactors, and phylogenetic information. The application of these criteria allows to systematically define, for the first time, the subfamily of atypical cyclins and enables the use of a common nomenclature for this extended family.

Keywords Phosphorylation · Cell cycle · Cyclin family · Canonical · Transcriptional

Introduction

It is 35 years, since cyclins were identified as proteins that exhibited a cyclic pattern of expression throughout the cell cycle of sea urchin eggs [1]. This major breakthrough, which garnered Tim Hunt the 2001 Nobel Prize in Physiology or Medicine, together with Lee Hartwell and Paul Nurse, placed cyclins at the core of the cell cycle clock: cyclins expressed at different points form complexes with cyclin-dependent kinases (CDKs), a family of conserved serine/threonine kinases that phosphorylate different substrates throughout the cell cycle in an orderly manner.

Interestingly, although it is believed that early eukaryotes already exhibited complex mechanisms of cell cycle regulation, the number of both CDKs and cyclins significantly increased during the process of evolution (for an extensive review of the phylogenetic origin and degree of conservation of CDKs and cyclins across different species, see [2]). Whereas *Saccharomyces cerevisiae* possesses six CDKs, the human genome codifies at least 20 CDKs, each characterized by a catalytic core comprising the ATP-binding pocket, the PSTAIRE-like cyclin-binding domain and an activating T-loop motif [3]. While some CDKs play cell cycle-related functions (the CDK1 and CDK4 subfamilies), others have been implicated in transcription regulation (CDK7-13 and CDK19-20) (for a review of CDK nomenclature and classification, see [4]).

In humans, CDKs are partners of more than 30 cyclins, a remarkably diverse group of proteins that were initially named, because their protein levels fluctuate in a cyclical fashion during the cell cycle. Currently, they are solely defined by the presence of a cyclin box domain (CBD) [3]. In this review, we aim to introduce additional criteria for the definition of "cyclin proteins".

The canonical CBD (PFAM 00134) is a sequence of approximately 100 amino acids arranged in five α-helices, and is responsible for binding and activation of CDKs [5–7]. Whereas all cyclins possess a CBD at the N-terminus half [8], some also exhibit an extra CBD (PFAM 02984 and PFAM 16899) which is thought to participate in protein folding [4, 9]. More recently, the C-terminal CBD of cyclin C was shown to mediate this cyclin's binding to Drp1

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GTPase, suggesting that the C-terminal CBD may be involved in CDK-independent functions [10]. In line with CDKs classification, cyclins have been traditionally divided in two groups, cell cycle (also frequently termed canonical) and transcriptional cyclins. The canonical cyclins (D, E, A, and B), which associate with cell cycle CDKs, were the first to be discovered and give the general name to the family [1]. The name canonical has been used by several authors working in different model organisms and pathologies [11–17] and reflects the fact that they share all the properties that originally defined cyclins: they are CDK activators that are periodically expressed and catabolized during different phases of the cell cycle [12]. They have also been named "cell cycle cyclins" [18], a designation that is better avoided as it excludes a "cell cycle" role for other cyclins (see below); moreover, it does not take into account that these cyclins regulate other aspects of the cell physiology beyond the cell cycle [19]. In contrast, the transcriptional cyclins (T, K, L, Q, C, and H) partner with transcriptional CDKs, and are mainly involved in the regulation of the RNA polymerase [20]; this designation has been broadly used by several groups working in the field [7, 11, 18, 21–25]. Nevertheless, although cyclins have been known by their ability to activate their partner CDKs, it is now recognized that either canonical or transcriptional cyclins carry out cellular functions that do not require the interaction with a CDK. For example, cyclin D1 may exert oncogenic actions through the stimulation of the transcriptional activity of estrogen receptors, independent of CDK4 [26], whereas cyclin C translocation to the cytoplasm promotes mitochondrial fission in yeast in response to stress [27].

However, over the last years, Genome Projects of different organisms unveiled the existence of several other proteins bearing a CBD [25], which remain poorly characterized. These novel members of the cyclin family have been named *new*, *orphan,* or *atypical* cyclins, reflecting different aspects of their distinctive features: the recentness of their discovery, the ignorance of their CDK partner, or some structural specificities, respectively. Moreover, proteins as diverse as the Transcription Factor IIB (TFIIB) or retinoblastoma (Rb) have an evolutionary distant CBD [5, 6] and, consequently, are unlikely to work as CDK activators. To further increase the complexity, it is now recognized that some proteins lacking the CBD are also able to activate CDKs, including viral cyclins, specific CDK5 activators, and RINGO/Speedy proteins. These CDK activators, which were the subject of an excellent review by Nebreda [28], lack the CBD that characterizes cyclins and, therefore, are out of the scope of this work, as discussed later in the manuscript.

Therefore, the state of the art in the field supports the need to revise the criteria that have been used to classify cyclins, in line with previous efforts to create a systematic nomenclature for CDKs [29].

In this review, we perform a comprehensive analysis of the human cyclin family. The identification of structural similarities and particular interactor patterns enabled us to revise the existing classification and propose a new one that includes the novel members of the family.

New cyclins: who is part of the family?

There is now a significant body of evidence that supports that both canonical and transcriptional cyclins are *bona fide* members of the cyclin family, as they bear a canonical CBD and they are known to be part of established CDK-cyclin complexes. These two groups of cyclins show significant conservation within the CBD region near residues K257 and E286 of CCNB1 (indicated by red dots in Fig. 1a), which were described to be critical for CDK binding in the six CDK/cyclin complexes that have known crystallographic models [30]. Indeed, mutation of this lysine in the CBDs of cyclin D1 and cyclin Y impairs the interaction with their respective CDK partners [30, 31]. A close look at this region reveals that there are also other well-conserved residues, of which there is less experimental evidence (Fig. 1a), and that transcriptional cyclins have a characteristic insertion between these two residues that is absent in canonical cyclins (Fig. 1a); such structural particularity may help to explain the specificity of interaction with distinct CDK subfamilies.

The defining Lys–Glu pair is remarkably conserved among the novel members of the cyclin family (Fig. 1b). Therefore, we propose that besides having a CBD (PFAM 00134, PFAM08613), a protein should contain the characteristic Lys–Glu pair to be considered a cyclin. Cyclin F (CCNF) does not have this critical Lys; it neither possesses the defining Glu nor the other surrounding conserved residues (Fig. 1c). For this reason, we consider that CCNF, which has been included in the family of F-box proteins [32], should not be part of the cyclin family, as it is unlikely that it interacts with a CDK. In line with these observations, the designation of F-box only protein 1 (FBXO1) would be a more adequate name for this protein, and has already been used in the literature [14, 33–35].

The unique exception is CCNG2, which does not present the characteristic Lys, but has another positively charged polar amino acid (Arg) instead; still, it presents the defining Glu and a significant degree of conservation on surrounding residues, in contrast to CCNF (Fig. 1) and, therefore, we consider that it should remain part of the family.

All the other potential cyclins analyzed conserve the defining Lys–Glu, suggesting that they are capable of interacting with CDKs and should thus be included in the cyclin family and named accordingly. Noteworthy, the majority of the novel members of the family present
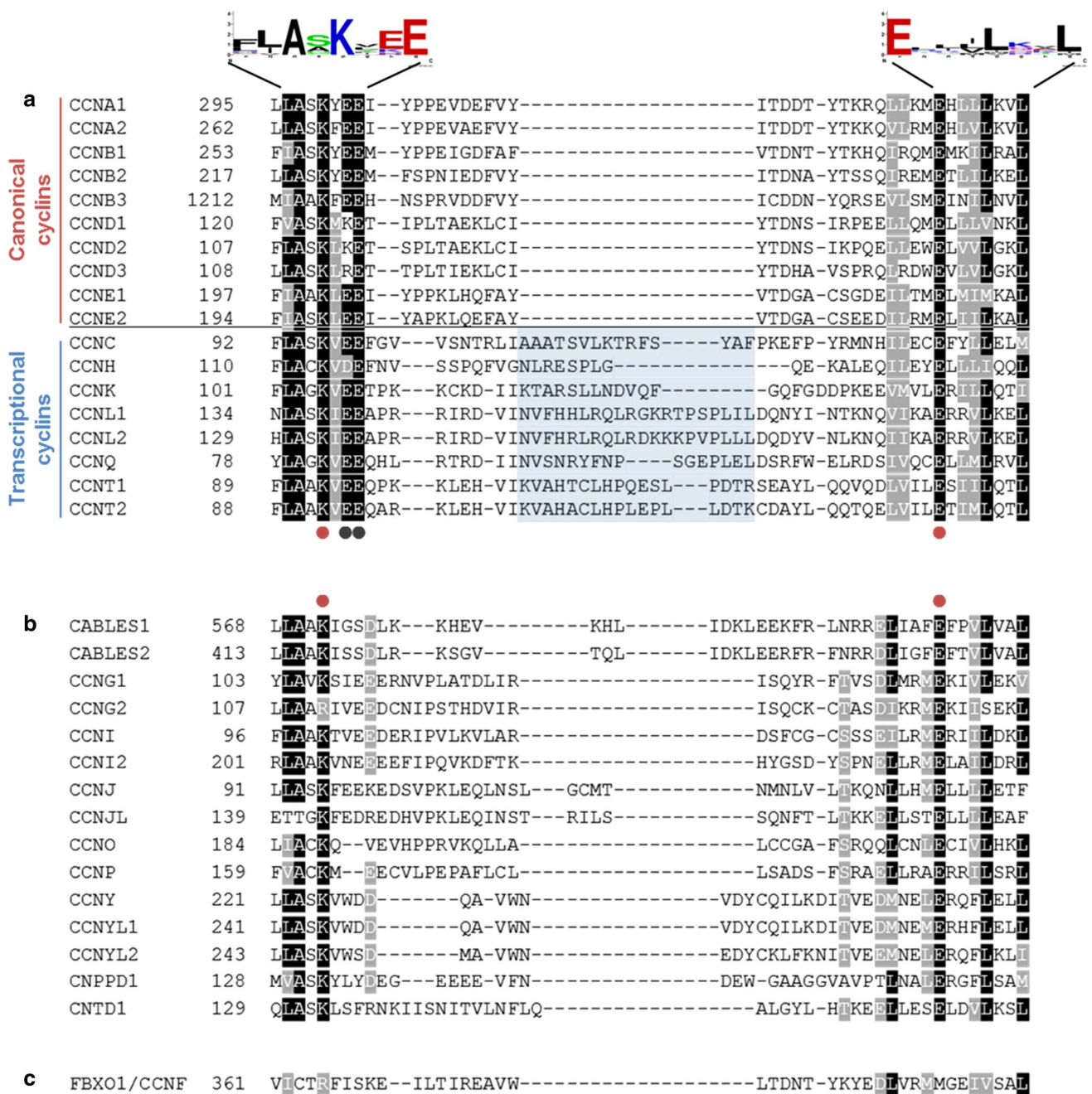
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                                    FILASKxEE                                          E...L.L.L
 a    CCNA1     295   LLASKYEEI--YPPEVDEFVY--------------------ITDDT-YTKRQLLKMEHLLLKVL
      CCNA2     262   LLASKFEEI--YPPEVAEFVY--------------------ITDDT-YTKKQVLRMEHLVLKVL
      CCNB1     253   FIASKYEEM--YPPEIGDFAF--------------------VTDNT-YTKHQIRQMEMKILRAL
      CCNB2     217   LLASKYEEM--FSPNIEDFVY--------------------ITDNA-YTSSQIREMETLILKEL
      CCNB3    1212   MIAAKFEEH--NSPRVDDFVY--------------------ICDDN-YQRSEVISMEININLNVL
      CCND1     120   FVASKMKET--IPLTAEKLCI--------------------YTDNS-IRPEELQMELLLLVNKL
      CCND2     107   FLASKLKET--SPLTAEKLCI--------------------YTDNS-IKPQELLEWELVVLGKL
      CCND3     108   LLASKLRET--TPLTIEKLCI--------------------YTDHA-VSPRQLRDWEVLVLGKL
      CCNE1     197   FIAAKLEEI--YPPKLHQFAY--------------------VTDGA-CSGDEILTMELMIMKAL
      CCNE2     194   FIASKLEEI--YAPKLQEFAY--------------------VTDGA-CSEEDILRMELIILKAL

      CCNC       92   FLASKVEEFGV---VSNTRLIAAATSVLKTRFS-----YAFPKEFP-YRMNHILECEFYLLELM
      CCNH      110   FLACKVDEFNV---SSPQFVGNLRESPLG-------------QE-KALEQILEYELLLIQQL
      CCNK      101   FLAGKVEETPK---KCKD-IIKTARSLLNDVQF--------GQFGDDPKEEVMVLERILLQTI
      CCNL1     134   NLASKIEEAPR---RIRD-VINVFHHLRQLRGKRTPSPLILDQNYI-NTKNQVIKAERRVLKEL
      CCNL2     129   HLASKIEEAPR---RIRD-VINVFHRLRQLRDKKKPVPLLLDQDYV-NLKNQIIKAERRVLKEL
      CCNQ       78   YLAGKVEEQHL---RTRD-IINVSNRYFNP----SGEPLELDSRFW-ELRDSIVQCELLMLRVL
      CCNT1      89   FLAAKVEEQPK---KLEH-VIKVAHTCLHPQESL---PDTRSEAYL-QQVQDLVILESIILQTL
      CCNT2      88   FLAAKVEEQAR---KLEH-VIKVAHACLHPLEPL---LDTKCDAYL-QQTQELVILETIMLQTL

 b    CABLES1   568   LLAAKIGSDLK---KHEV--------KHL-------IDKLEEKFR-LNRRELIAFEFPVLVAL
      CABLES2   413   LLAAKISSDLR---KSGV--------TQL-------IDKLEERFR-FNRRDLIGFEFTVLVAL
      CCNG1     103   YLAVKSIEEERNVPLATDLIR-------------------ISQYR-FTVSDLMRMEKIVLEKV
      CCNG2     107   LLAARIVEEDCNIPSTHDVIR-------------------ISQCK-CTASDIKRMEKIISEKL
      CCNI       96   FLAAKTVEEDERIPVLKVLAR-------------------DSFCG-CSSSEILRMERIILDKL
      CCNI2     201   RLAAKVNEEEEFIPQVKDFTK-------------------HYGSD-YSPNELLRMELATLDRL
      CCNJ       91   LLASKFEEKEDSVPKLEQLNSL---GCMT-----------NMNLV-LIKQNLLHMELLLLETF
      CCNJL     139   ETTGKFEDREDHVPKLEQINST---RILS-----------SQNFT-LIKKELLSTELLLEAF
      CCNO      184   LIACKQ--VEVHPPRVKQLLA--------------------LCCGA-FSRQQLCNLECIVLHKL
      CCNP      159   FVACKM--EECVLPEPAFLCL--------------------LSADS-FSRAELLRAERRILSRL
      CCNY      221   LLASKVWDD-------QA-VWN---------------VDYCQILKDITVEDMNELERQFLELL
      CCNYL1    241   LLASKVWDD-------QA-VWN---------------VDYCQILKDITVEDMNEMERHFLELL
      CCNYL2    243   LLASKVWSD-------MA-VWN---------------EDYCKLFKNITVEEMNELERQFLKLI
      CNPPD1    128   MVASKYLYDEG---EEEE-VFN---------------DEW-GAAGGVAVPTLNALERGFLSAV
      CNTD1     129   QLASKLSFRNKIISNITVLNFLQ----------------ALGYL-HIKEELLESELDVLKSL

 c    FBXO1/CCNF 361  VICTRFISKE--ILTIREAVW-------------------LTDNT-YKYEDLVRVMGEIVSAL
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Fig. 1 Conservation of critical residues for CDK binding. Multiple sequence alignment of the cyclins region critical for CDK binding [30] was conducted using *Jalview* software set to *Clustal Omega*. The resulting alignment (manually refined) was grouped into canonical and transcriptional cyclins (**a**) as they are considered *bona fide* cyclins, or potential cyclins (**b**) and exported to *ExPASy BoxShade* to highlight conservation (black boxes = conserved). **c** Cyclin F (CCNF)/F-box only protein 1 (FBXO1) sequence alignment. Logos for cyclin consensus sequences were identified using WebLogo [112]. Red dots indicate the Lys–Glu pair conserved among cyclins; gray dots indicate the Glu–Glu pair that is only present in canonical and transcriptional cyclins. Aminoacid sequences were retrieved from UniProt; positions of the N-terminal cyclin boxes used for the alignment were retrieved from Pfam, a database of curated protein families defined by multiple sequence alignments and hidden Markov model profiles [113]

some particularities in their sequences, such as the lack of the double glutamic acid (indicated by two gray dots in Fig. 1a) located in close proximity to the defining Lys of both canonical and transcriptional cyclins. Although it is not yet clear how this distinctive feature affects the interaction with a CDK, it is tempting to speculate that these cyclins might interact with different CDKs. Therefore, we will tentatively name all the new members of the family as

atypical cyclins, a matter that is further discussed throughout the manuscript.

A no less important issue is the nomenclature of atypical cyclins. Whereas canonical cyclins were named by alphabetical order of appearance, the names of some atypical cyclins have a tortuous history, and some of these proteins even had several names at the same time, as demonstrated by the following examples. First, CCNL2 was previously known as CCNS, described as having a high homology to CCNL [36]; they are now considered isoforms. Second, the cyclin that was originally named CCNP by Murray and Marks [25] disappeared from the repositories after successive annotations; later, it was annotated again in the human genome but with a new name, CNTD2. The use of CCNP is also accepted by the HUGO Genome Nomenclature Committee (https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:25805). Given that at the present moment, there are only five PubMed entries using this name, we propose that CCNP should again be considered as the first name option. Third, CCNQ has been named FAM58A and cyclin M, a designation that should be avoided given that it is still used to refer to metal transporters, which were initially named Cyclins M1-4. Finally, CCNY isoform 3 was formerly known as CCNX [37].

Human cyclin interactors: who is my CDK partner?

Consistent with the distinctive features of the region that determines CDK binding (Fig. 1), canonical and transcriptional cyclins interact with different CDKs (Fig. 2). Canonical cyclins have interactors among the CDK1- and CDK4-related subfamilies, which is coherent with their role in cell cycle regulation, while transcriptional cyclins interact with transcriptional CDKs from subfamilies 7, 8, 11, 9, and 20, as expected from their functional role (Fig. 2).

In contrast to the previous ones, a significant number of atypical cyclins remain "orphan", with no known partner CDK, a term that was used to refer to "orphan CDKs". Interestingly, when an interactor for the atypical cyclin has been identified, it belongs to the CDK5-related subfamily (Fig. 2), a group that includes the so-called atypical CDKs: 5, 14, 15, 16, 17, and 18 [4]. This predilection for the CDK5 subfamily of CDKs suggests that the "atypicals" are likely to play roles that go beyond mere redundancy with the other subfamilies of cyclins, participating in specific cellular processes. Nevertheless, this hypothesis is limited by the absence of studies that systematically address the interactions between cyclins and CDKs, and it is possible that more complexes are yet to be identified.

Structural identity of human cyclins

The identity of the N-terminal CBD was selected to establish the relationships between family members, given that this is the most conserved region [8]. With this type of analysis (Fig. 3), the transcriptional cyclins emerge as a group with a clear identity in line with previous alignments [2, 11, 38]. Also as described, all the canonical cyclins present high homology in their CBD. Interestingly, some of the atypical cyclins (O, P, G, and I) have a CBD closely related to canonical cyclins, whereas the other atypical members seem more distant, suggesting that atypical cyclins might have different evolutionary origins.

Cyclins architecture is highly variable in terms of length, with some members presenting extensions on either the N- or the C-terminals of the CBDs (Fig. 3). Most remarkable is the fact that although closely related in terms of sequence identity of the N-terminal CBD, the majority of atypical cyclins present a single CBD, while all the members of the canonical subfamily have two.

At that point, we propose to establish the new subfamily of atypical cyclins whose members should fulfill at least two of the following criteria: they present a specific context of amino acids in the vicinity of the defining Lys–Glu pair (Fig. 1); they are still "orphans" or interact with atypical CDKs (Fig. 2); and they only have one CBD (Fig. 3).

Atypical cyclins for novel functions?

After establishing the new subfamily of atypical cyclins, the analysis of their main functions may eventually shed some light on the need to have additional cyclins.

Early studies demonstrated that CABLES1 is located in chromosome 18q, which is commonly lost in colon cancer [39], suggesting that CABLES1 played an important role in this malignancy. Indeed, later studies demonstrated that loss of CABLES1 enhanced tumor progression in the Apc(Min/+) mouse model, which may be a consequence of increased activation of the Wnt/β-catenin pathway [40]. It was also shown that CABLES1 overexpression induced apoptosis and inhibited cell growth at least in part through p21 stabilization [41, 42], further consolidating that CABLES1 acts as a tumor suppressor. Moreover, CABLES1 has been shown to protect p63 from proteasomal degradation, modulating its function during genotoxic stress [43]. The role of CABLES1 in cancer was recently revised by Huang et al. [44]. Interestingly, CABLES1 has been mostly regarded as an adaptor protein and most studies have not addressed the relevance of its interaction with CDKs for its cellular functions.

	Cell Cycle					Atypical						Transcriptional									
	CDK1			CDK4		CDK5							CDK8		CDK11			CDK9		CDK20	
	CDK1	CDK2	CDK3	CDK4	CDK6	CDK5	CDK14	CDK15	CDK16	CDK17	CDK18	CDK7	CDK8	CDK19	CDK10	CDK11A	CDK11B	CDK9	CDK12	CDK13	CDK20
Canonical CCNA1	(a)	(a)																			
CCNA2	(a)	(a)																			
CCNB1	(a)																				
CCNB2	(a)																				
CCNB3	(a)																				
CCND1				(a)	(a)																
CCND2				(a)	(a)	(b)															
CCND3				(a)	(a)	(b)															
CCNE1		(a)																			
CCNE2		(a)																			
Atypical CABLES1						(b)															
CABLES2						(b)															
CCNG1						(c)															
CCNG2																					
CCNI						(d)			(e)												
CCNI2						(f)															
CCNJ																					
CCNJL																					
CCNO																					
CCNP																					
CCNY							(a)		(a)												
CCNYL1									(e)												
CCNYL2																					
CNPPD1																					
CNTD1																					
Transcriptional CCNC			(a)										(a)								
CCNH												(a)									
CCNK																		(a)	(a)	(a)	
CCNL1																(a)	(a)				
CCNL2																(a)	(a)				
CCNQ															(g)						
CCNT1																		(a)			
CCNT2																		(a)			

Fig. 2 CDK–cyclin interactions. Cyclins were grouped into canonical, transcriptional, and atypical cyclins, whereas CDKs were grouped into cell cycle, transcriptional, and atypical CDKs as described by Malumbres, 2014 [4]. The table shows the reported CDK–cyclin interactions. For atypical cyclins, a systematic search in the STRING database was conducted [114]. Only the interactions supported by experimental data were selected and further revised for confirmation. **a** reviewed in [3]; **b** [115]; **c** [54]; **d** [66]; **e** [84]; **f** [70]; **g** [116]

In contrast to CABLES1, the role of CABLES2 has been much less investigated. However, an early report suggests that it may also act as a proapoptotic factor, via both p53-dependent and independent pathways [45]. Although it was reported that the CBD plays a role in CABLES2-induced apoptosis [45], it was not fully demonstrated that these effects are mediated through binding to CDK5, which was described as its main CDK partner [46].

CCNG1 transcription is activated by p53 [47, 48], which is consistent with its proposed role in apoptosis and growth inhibition [49, 50]. Likewise, CCNG1 decreased the proliferation of human endometrial cells [51] and increased sensitivity to radiation [52]. CCNG1 also works as a negative regulator of p53 through binding to PP2A and consequent Mdm2 dephosphorylation [53]. It was also reported that

CCNG1 rendered lung cells more susceptible to DNA damage by upregulating cyclin B1 [52]. It was later proposed that CCNB1 transcription was upregulated by the CCNG1/CDK5 complex via phosphorylation of c-Myc on Ser-62 [54]. The evolving function of CCNG1 and its potential as therapeutic target in cancer have been the object of a recent review by Al-shihabi et al. [12].

CCNG2 was shown to inhibit cell cycle progression by binding to PP2A (through a region outside the CBD) and modulating centrosomal-associated activities [55, 56]. CCNG2 was also implicated in cell differentiation by promoting syncytiotrophoblast differentiation [57] and terminal differentiation at the site of blastocyst after implantation [58]. Moreover, CCNG2 inhibits cancer stem cell-like properties and suppresses the epithelial-to-mesenchymal
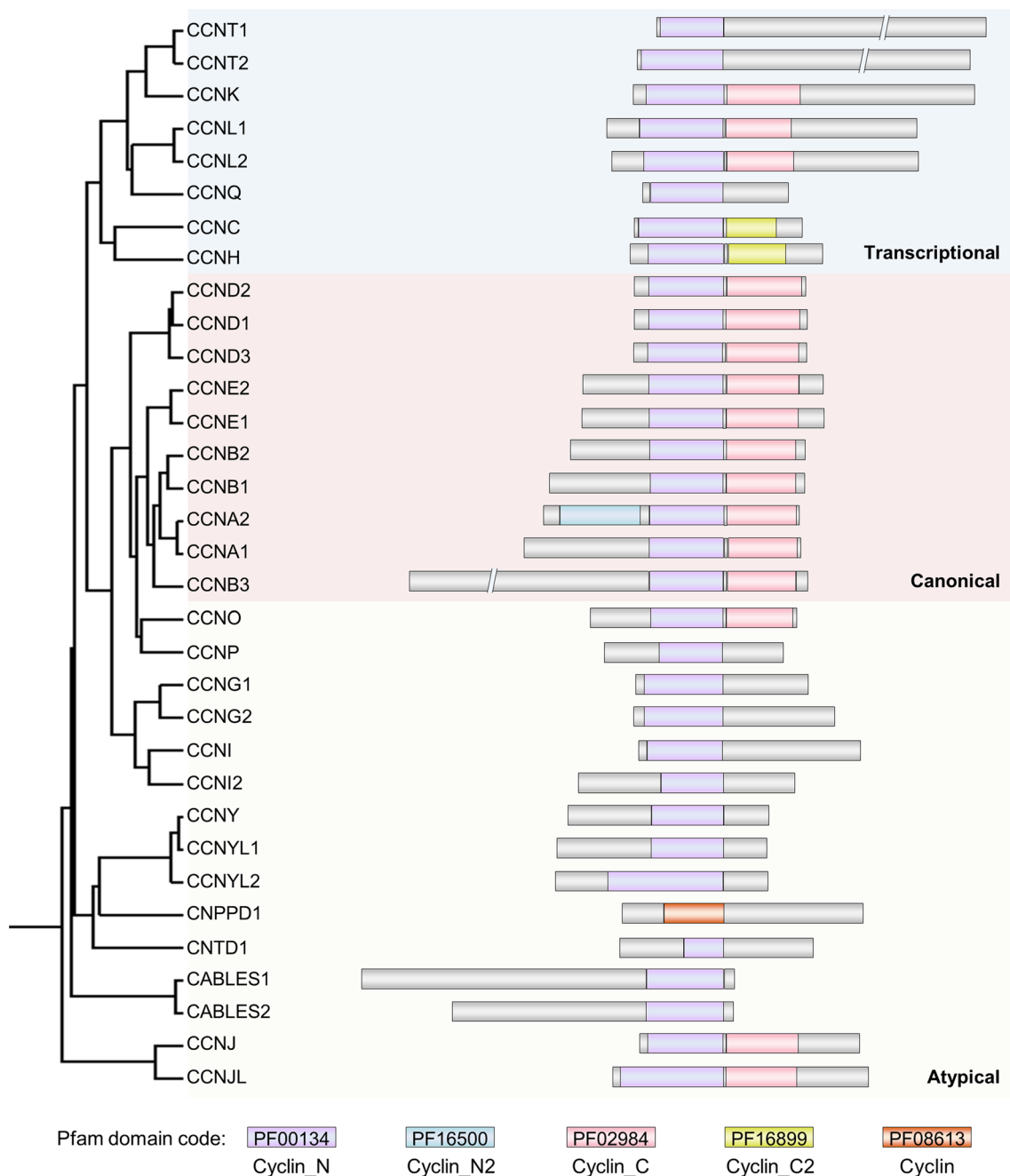
Fig. 3 Human cyclin proteins. Sequence-based phylogenetic tree of human cyclins. The tree was generated by bootstrap analysis of the N-terminal cyclin box amino acid sequence using *Clustal Omega*. All the proteins containing either a Pfam domain PF00134 or PF08613 were included in the analysis. The length of the proteins, as well as the length of the domains, are on scale

transition by attenuating Wnt signaling [59, 60]. CCNG2 downregulation was also associated with chemoresistance [60]. Consistent with its tumor suppressive role, which has been associated with lower CDK2 protein levels, the expression of CCNG2 is downregulated in several human cancers, and correlates with a worse clinical prognosis [61–64].

CCNI was shown to regulate the survival of podocytes, which are essential for the integrity of kidney glomeruli

[65]. The prosurvival function of the CCNI-CDK5 complex was shown to occur via MEK/ERK pathway activation and upregulation of antiapoptotic Bcl-2 and Bcl-XL [66]. CCNI has also been shown to increase the proliferation of Hela and lung cancer cell lines, although it is still unclear whether these effects are mediated through the interaction with a CDK [67, 68]. Accordingly, CCNI overexpression was associated with a worse prognosis in patients with lung

adenocarcinoma [67] and it was proposed that CCNI mRNA in saliva could be a biomarker for lung cancer detection [69].

CCNI2 was recently shown to regulate cell proliferation, acting as a CDK5 activator, similarly to CCNI [70]. It was proposed that CCNI and CCNI2 compete for binding to CDK5, determining distinct subcellular localizations [70]. Considering that CDK5, in addition to its protective role in neuronal tissue [71], is implicated in the initiation and progression of neuroendocrine thyroid cancer [72], it would be interesting to explore the differential function of these complexes in the context of cancer and uncover potential strategies targeting CDK5-mediated oncogenic signaling.

It was reported that CCNO is expressed in the cytoplasm of multiciliated cells, critical for mucociliary clearance, acting downstream of multicilin [73]. Cells with impaired CCNO expression display a marked reduction in the number of multiple motile cilia, which is caused by altered generation of centrioles at deuterosomes [73, 74]. Therefore, it is not surprising that several studies have assigned CCNO a role in multiciliogenesis and mucociliary disorders [73–78] and infertility [79]. CCNO has also been shown to promote apoptosis in lymphoid cells [80].

Recent work from our group demonstrated that CCNP, also known as CNTD2, is overexpressed in samples from lung and colon cancer patients and promotes tumor cell proliferation and migration both in vitro and in vivo [67, 81]. Further studies are now required to provide insight on the mechanisms underlying the oncogenic actions of CCNP. Apart from these studies, it is only known that CCNP enhances viral replication [82] and correlates with the expression of Epstein–Barr virus genes [83].

CCNY was shown to be essential for spermatogenesis [84] and to play a role in cytoskeleton regulation either in complex with CDK16 [85] or CDK14, the latter involving activation of non-canonical Wnt signaling [86]. The ability of CCNY to activate Wnt signaling was also shown to be critical for maintenance of progenitor cell properties during cell division [87]. Recently, it was reported that the CDK16/CCNY complex increased the proliferation of several cancer cell lines through the phosphorylation of the protein regulator of cytokinesis 1 (PRC1) [85]. Despite this role in cell proliferation, CCNY is also expressed in neurons, where it is associated with several functions, including the regulation of synaptic plasticity [88, 89].

Like CCNY, CCNYL1 has been implicated in the maintenance of stem cell properties by activating Wnt signaling in mitosis [87]. CCNYL1, in complex with CDK16, was also implicated in spermatogenesis [90], a finding that may also reflect its ability to modulate Wnt signaling [91].

Regarding CNTD1, it was shown to be critical for meiotic crossover maturation by regulating the association between HEI10 and RNF212 and components of the crossover machinery [92].

Remarkably, the role of some atypical cyclins remains largely unexplored. This is the case of CNPPD1, which is mentioned as a gene candidate for schizophrenia susceptibility in the Japanese population [93]. More recently, CNPPD1 was proposed as a neoantigen in breast cancer lymph node metastasis [94]. Regarding CCNJ, it is known to be repressed by tumor suppressor microRNAs in breast, gastric, prostate, and bladder cancers [95–98]. At the present moment, there are no entries in PubMed that may shed some light on the roles of either CCNYL2 or CCNJL.

Whereas the functions of most atypical cyclins are still poorly characterized, many of them have also been implicated in key cellular processes that have been attributed to canonical cyclins [19], such as cell proliferation and differentiation, or response to DNA damage (Table 1). Although this review focuses on human proteins, we have confirmed that most of the cyclins are conserved among mammals (not shown). Moreover, some atypical cyclins, such CCNYs (named PCLs in yeast), are conserved in unicellular eukaryotes. Such high degree of conservation is consistent with an essential role [2]. Interestingly, some atypical cyclins appeared later in evolution (CCNG1/I, CCNJ, or CCNO), but so did some canonicals, such as CCNA [2], suggesting that these late-appearing atypical cyclins may perform specific functions rather than being mere accessories to the normal cell physiology.

Further studies are now needed to fully characterize the roles of atypical cyclins in the physiological context. The recent observation that embryonic stem cells are able to proliferate in the absence of G1 cyclins [99], suggests that other (perhaps atypical) cyclins may be able to drive cell cycle progression in this cellular model. On the other hand, while additional cyclins are likely to be advantageous in a physiological context by providing additional regulatory flexibility, such diversity may actually be deleterious in a pathological context. For instance, the complexes of CCNY with either CDK14 or CDK16 have been shown to increase cell proliferation [85, 100, 101], suggesting that at least some atypical cyclins can use alternative CDKs to foster cell proliferation. Furthermore, atypical complexes may provide an escape route to the inhibitory actions of anticancer agents, in agreement with the observation that CCNG1 downregulation increased sensitivity to doxorubicin [102] or paclitaxel [103].

Concluding remarks

The complexity of the cyclin family increased dramatically over the last 2 decades. With so many cyclins, it became unclear what defines cyclins and how new members can be integrated in this family.

Table 1 Main functions of atypical cyclins

Cyclin	Function	Main references
CABLES1	Modulation of response to genotoxic stress	[43]
	Regulation of cell proliferation and apoptosis	[40–42]
CABLES2	Apoptosis promotion	[45]
CCNG1	Participation in response to DNA damage	[117–119]
	Regulation of cell proliferation and apoptosis	[49, 50]
	Regulation of cell cycle progression	[55, 56]
CCNG2	Regulation of cell differentiation	[57–59]
	Regulation of DNA damage response	[120, 121]
CCNI	Protection of kidney podocytes from apoptosis	[65, 66]
	Regulation of cell cycle progression	[67, 68]
CCNI2	Regulation of cell cycle progression	[70]
CCNO	Apoptosis induction in lymphoid cells	[80]
	Regulation of deuterosome-mediated amplification of centrioles in multiciliated cells	[73, 74]
CCNP	Regulation of cancer cell proliferation	[67, 81]
	Modulation of viral replication	[82]
	Regulation of spermatogenesis	[84]
CCNY	Regulation of neuronal function	[88, 89, 122]
	Maintenance of stem/progenitor cell properties	[87]
	Regulation of cytoskeleton and cell proliferation	[85, 86]
CCNYL1	Regulation of spermatogenesis	[90, 91]
	Maintenance of stem/progenitor cell properties	[87]
CNTD1	Essential for meiotic crossover maturation	[92]

Cyclins owe their name to their cyclic pattern of expression [1]; this defining trait soon failed to embrace the distinct expression pattern of transcriptional cyclins, the levels of which do not oscillate. On the other hand, cyclins have been defined by their biological roles in cell cycle or transcriptional regulation, which seems to be overly simplistic given that "cell cycle" cyclins also modulate transcription [19]. Therefore, our classification is based on the presence of a Lys–Glu pair that is known to be critical for interaction with a CDK (Fig. 1). It is important to highlight that our criteria for inclusion in the cyclin family were mostly based on structure, rather than function (ability to activate CDKs); this way, proteins that lack the characteristic N-terminal CBD were excluded from this analysis, even though they may work as CDK activators. For example, p35, a known activator of CDK5 lacks significant sequence homology with cyclins [28]. Another example would be the RINGO/Speedy proteins that, in spite of lacking a CBD, are also able to activate CDK1 and CDK2 [28, 104, 105]. The fact that CDK activation by RINGO/Speedy proteins is CAK1 independent [28, 106, 107], suggests that their activation mechanism is distinct from the one used by canonical cyclins. This observation, together with their structural particularities, led several authors to define a RINGO/Speedy box that is clearly distinct from the CBD, supporting their exclusion from the cyclin family.

The application of our criteria reinforces the existence of the canonical and the transcriptional cyclin subfamilies, designations that have been widely used in the literature. Moreover, our analysis allowed us to define, for the first time, the family of atypical cyclins. Although atypical cyclins have been mentioned by several groups [66, 81, 103, 108, 109], they were never object of a comprehensive analysis to establish whether they could actually be included in the cyclin family or what defined them as atypical. We believe that the name atypical is the one that more accurately reflects the particularities of these cyclins and has already been used by several groups [66, 81, 103, 108, 109]. Other names, such as "new cyclins" [110] or "orphan cyclins" [67, 111], are not recommended given that after all these years, they can hardly be considered new, whereas some previously orphan cyclins have now known CDK partners.

According to our analysis, atypical cyclins are characterized by three main aspects. One is the presence of the defining Lys–Glu pair in a context that is different from the double glutamic context observed in both canonical and transcriptional cyclins (Fig. 1). This distinctive context may explain the second aspect that characterizes atypical cyclins, which is the absence of interactors or the interaction with atypical CDKs (Fig. 2). The third aspect is the presence of a single CBD (Fig. 3). Although there are exceptions and, thus, none of these criteria is able to define atypical cyclins

per se, when applied altogether, they reinforce the existence of a cyclins subfamily with distinctive features, supporting the choice for the name atypical.

Moreover, the interactor landscape suggests that atypical cyclins mostly interact with members of the subfamily of CDK5, which was considered the prototype of atypical CDKs [4]. Therefore, this update on cyclins nomenclature leads to a significant convergence with standing CDK nomenclature.

Whereas transcriptional cyclins clearly differ from other cyclins in the region that determines CDK binding (Fig. 1) or structural identity (Fig. 3), the line that separates canonical and atypical cyclins is much fainter. This observation is in line with the fact that canonical and atypical CDKs are also more closely related with each other than with transcriptional CDKs [4]. Given that atypical cyclins have not been thoroughly characterized, cyclin classifications are likely to evolve and cyclins that are now considered atypical may become canonical. Indeed, the similarities between atypical and canonical cyclins go beyond structural identity, as both have been implicated in the regulation of cell proliferation. Moreover, a closer look at this subfamily may unravel novel strategies to fight cancer. In this regard, our group has recently assigned an oncogenic role to CNTD2/CCNP in colon and lung cancers [67, 81]. Given that CCNP is overexpressed in several cancers and poorly expressed in tissues, it may represent the ideal target candidate. Further studies are now warranted to establish the physiological functions of atypical cyclins and understand their potential as therapeutic targets in cancer.

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