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REVIEW

CDKs Family -a Glimpse into the Past and Present: From Cell Cycle Control to Current Biological Functions

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Abstract

Cyclin-dependent kinases (CDKs) are the catalytic subunits or protein kinases characterized by separate subunit "cyclin" that are essential for their enzymatic activity. CDKs play important roles in the control of cell cycle progression, cell division, neuronal function, epigenetic regulation, metabolism, stem cell renewal and transcription. However, they can accomplish some of these tasks independently, without binding with cyclin protein or kinase activity. Thus, so far, twenty different CDKs and cyclins have been reported in mammalian cells. The evolutionary expansion of the CDK family in mammals led to the division of CDKs into three cell-cycle-related subfamilies (Cdk1, Cdk4 and Cdk5) and five transcriptional subfamilies (Cdk7, Cdk8, Cdk9, Cdk11 and Cdk20). In this review, we summarizes that how CDKs are traditionally involve their latest revelations, their functional diversity beyond cell cycle regulation and their impact on development of disease in mammals.

Keywords: Cyclin-dependent kinases- cell cycle- human cancer

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Introduction

The cellular processes such as cell cycle is driven by protein kinases referred to as "Cyclin dependent kinases" (CDKs) whose serine/threonine-specific catalytic core, control the kinase activity and are only activated when bound by specific regulatory subunit "cyclin". This CDKs activity is regulated by phosphorylation of a target protein through CDK's T-loop and binding of inhibitory proteins [1].

CDKs were first discovered through biological and genetic studies in yeast [2-5]. In human, there are twenty distinct family members of CDKs have been described, which have been involved in two main process transcription and cell division between distinct phases of the cell cycle through specific substrate phosphorylation [6-7].

In this review, we first summarize the most relevant information for known CDKs, with a particular emphasis on those involved in regulating the cell cycle. We then discuss other observations derived from biological studies based on animals and human models.

In 1987 first human kinases, CDK1 was cloned by using functional complementation in yeast, and was termed cell division cycle 2 (Cdc2) because of its high homology with fission yeast kinase Cdc2. CDK1 bind to cyclin A and B and encoded by the Cdc2 gene [2], these complexes drive the transition between G2 phase and M phase, as well as early M phase.

Discussion

In higher eukaryotes, CDK1 and CDK2 emerged as key determinant of mitotic progression and DNA replication respectively. However, they regulate the G1/S and G2/M phases of the cell cycle by binding with cyclin E or A and cyclin B kinase, respectively [8]. Cyclin E binds G1 phase Cdk2, which is required for the transition from G1 to S phase while binding with Cyclin A is required to progress through the DNA synthetic S phase (Figure 1).

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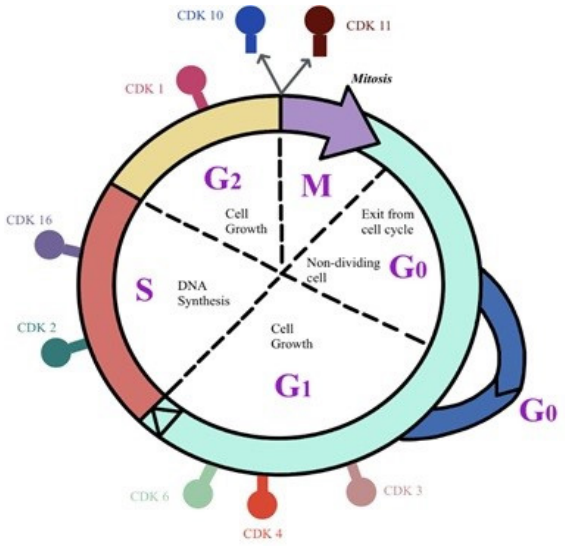

Figure1. Function of CDKs and Cyclin (CDK/Cyclin) Complexes at Specific Phases of the Cell Cycle.

Previous study has revealed biological role of CDK2 in cellular proliferation, cell death, and DNA repair in human embryonic stem cells (HESC) [9]. A recent study by Mori et al [10] showed Cep169, a centrosomal protein conserved among vertebrates, dissociation is controlled by Cdk1/Cyclin B during mitosis.

CDK3 is the closest relative to CDK2 among mammalian CDK genes identified thus far and has originally been classified as a cyclin dependent kinase, because of its high sequence identity with CDK2 and the ability to complement cdc28 mutations in yeast [11]. It executes an essential function at the G1/S transition (Figure 1) in the mammalian cell cycle (van den Heuvel 1993). CDK3 binds with Cyclin C and regulate the Rb-dependent G0/G1 transition [12] while enhancing the transactivation and transcriptional activities of the transcription factor 1 (TF1) by phosphorylation [13].

Previously it was revealed that CDK4 and CDK6 are dispensable for cell cycle progression and are essential for development and differentiation of highly specialized cell types [14]. However, recently Sherr CJ and his group reported their roles in mammalian cell proliferation, where they help to drive the progression of cells into the S phase of the cell division cycle (Figure 1) [15]. Through association and activation of CDK4 and CDK6 with D-Type cyclins, promotes progression to G1 phase, however, CDK4 inhibition has been shown to induce G1 arrest and apoptosis [16-17].

In addition, CDK4 and CDK6 are also involved in promoting cell death in neurons during development and disease. CDK4 has been known in the regulation of neuronal cell death, while activation of CDK4 leads to hyper-phosphorylation of the pRb family member p130, dissociation of p130 and associated chromatin modifiers from the transcription factor E2F4. However, pro-apoptotic BH3-only protein Bim, (Bcl-2-like protein 11) is stimulated by expression of E2F binding genes including the transcription factors B- and C-Myb (myeloblastosis) [18]. Previously it was also reported that deregulation of CDK4 and CDK6 kinase with cyclin D resulting in Rb hyperphosphorylation associated with a loss of control between mitogenic stimuli and cell cycle regulation, which leads to uncontrolled cell proliferation and apoptosis (Figure 2) [19].

CDK5 is unusual because it is not believed to be active in a typical cell cycle while it binds to cyclin protein. It is well characterized for its role in the central nervous system, terminally differentiated and proliferating cells rather than in the cell cycle [20]. Recent study showed Cdk5-ATM (ataxia-telangiectasia mutated) pathway plays a crucial role in DNA damage-induced neuronal injury [21]. It was previously reported that Cdk5 retards closure of an in vitro scrape wound in a mouse corneal epithelial cell line and strengthens cell-matrix adhesion and possible biological function of CDK5 described in Figure 3 [22].

Subsequently, CDK7, CDK8 and CDK9 were identified and are known to directly promote the cell cycle

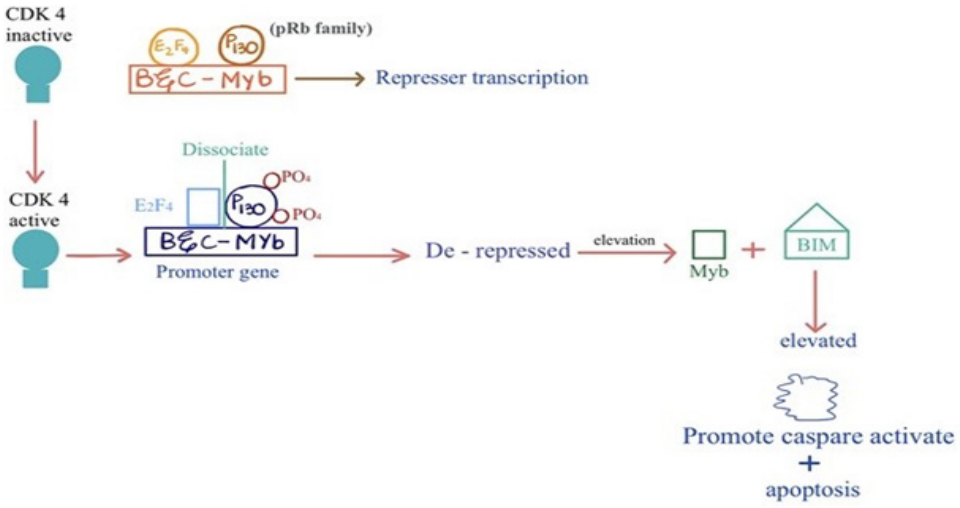

Figure 2. CDK4 Involvement in Neuronal Cell Death

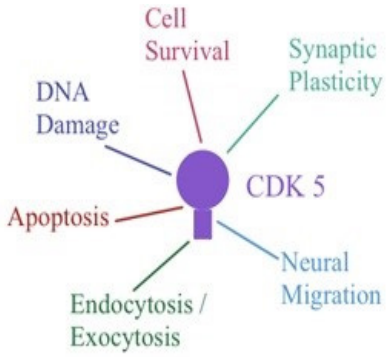

Figure 3. Diverse Biological Function of CDK5.

and regulate the transcription [23-25]. CDK7 associates with Cyclin H and forms a complex termed CAK, the CDK-Activating Kinase, this complex phosphorylate cell-cycle CDKs within the activation segment (T-loop), and also a component of the general transcription factor TFIIH, which phosphorylates the C-terminal domain (CTD) of Pol II [26] (Figure 4a).

Another function of CDK7 emerged in neocortical development and proper expression levels of both CDK7 and miR-210 are required for normal Neural Progenitors cell-cycle progression [27]. In addition, CDK8 as part of mediator complex, regulates gene expression through phosphorylation of transcription factors [28]. Moreover, this complex controls the Mediator–pol II interaction to help in the transcription initiation and reinitiating events which are required for expression of protein-coding genes, this may reflect a common mechanism in the human cells by which activated transcription is shut down [29] (Figure 4b). Moreover, it is also required for cell division associated with Wnt/ β-catenin signaling (Figure 4c), [30-31] and act as a novel regulator of p27 by facilitating Skp2 (S-phase kinase-associated protein 2)-mediated ubiquitination and degradation of p27 in breast cancer [32].

Cyclin T1, T2a, T2b, or K associates with CDK9 to form active positive transcription elongation factor (P-TEFb) complexes, resulting in activation of the transcriptional elongation by phosphorylating the C-terminal domain (CTD) of RNA polymerase II (Figure 4 d) (RNAPII) [33-34]. Previously it has also been reported that CDK9 predominantly involved in co-transcriptional histone modification, messenger RNA (mRNA) processing, mRNA export and DNA repair [35].

CDK10 was discovered by sequence homology screening for CDK-related genes and plays a role in the cell cycle through acting during the G2 or M phase (Figure 1) [36]. Currently, it was reported that it acts as the regulator of the ETS2 transcription factor and modulates its transactivation activity (Figure 4 e) [37]. However, for the past twenty years and until recently, the elucidation of the functions of CDK10 was hampered by the lack of any identified cyclin partner. Guen etal has reported siRNA mediated silencing of cyclin M causes extreme reduction of CDK10 expression in human cells [38]. In addition, several studies have shown reduced expression of CDK10 in many cancer, demonstrating its putative role as tumor suppressor gene in multiple types of human cancers [39-42].

CDK11 binds with cyclins L and has role in transcription, RNA processing in particular alternative splicing [43-45]. It is also participates in many other pathways, such as hormone receptor signaling or

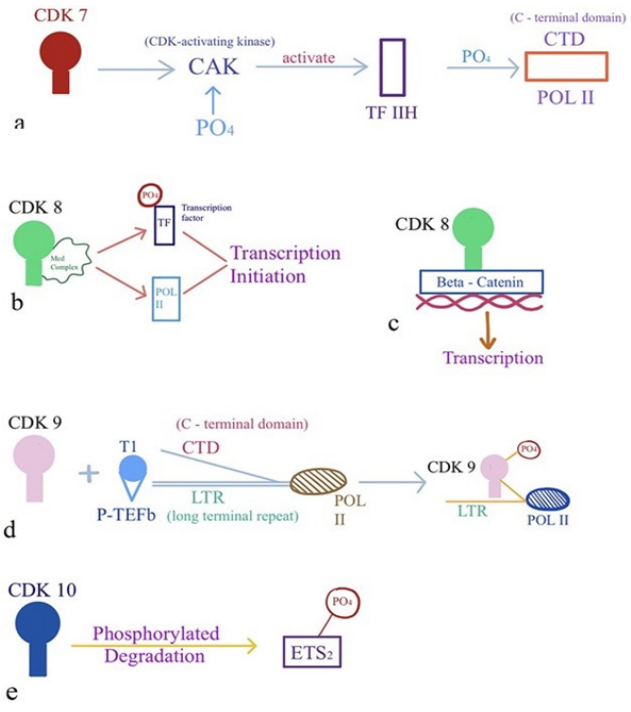

Figure 4. Biological Activity of CDKs (a) CDK7, (b and c) CDK8, (d) CDK9, (e) CDK10

Table 1. Cellular Function of CDKs

Protein	Cyclin binding element	Cyclin	Kinase Activity	Cellular Function	References
CDK1	PSTAIRE	A & B	Yes	Control G2 & M Phase, FoxM1 and FoxK2 transcription in complex with cyclin B, ESC self-renewal through interaction with Oct4, NSC self-renewal through inhibition of Ngn2, HR-mediated DNA damage repair, Epigenetic regulation through Ezh2 and Dnmt1, dissociation of Cep169 from centrosomes is controlled by Cdk1/Cyclin B during mitosis	(10, 36, 55)
CDK2	PSTAIRE	E & A	Yes	Control of G1-S Phase of cell cycle Promote S phase entry by USP37 activation Myoblast proliferation through inhibition of MyoD Rb/E2F transcription FoxM1 and FoxK2 transcription in complex with cycA NSC self-renewal through inhibition of Ngn2 Epigenetic regulation through Ezh2 and Dnmt1	(55, 83)
CDK3	PSTAIRE	C		NHEJ-mediated DNA damage repair in complex with cyclin C	(14, 15, 84)
CDK4	PISTVRE	D	Yes	Control G 1 Phase of cell cycle, Rb/E2F transcription Epigenetic regulation through Mep50	
CDK5	PSSALRE	None	Yes	Activated by non-cyclin proteins, including Cdk5R1 (p35) and Cdk5R2 (p39), Neuronal function in complex with p35 and p39, Epigenetic regulation through Dnmt1, Glycogen synthesis Strengthens cell-matrix adhesion and retards closure of an in vitro scrape wound in a mouse corneal epithelial cell line	(22)
CDK6	PLSTIRE	D	Yes	Control of G1 Phase of cell cycle; Rb/E2F Transcription progression of cells into the DNA synthetic (S) phase	
CDK7	NRTALRE	H	Yes	Cdk-activating kinase (CAK) and RNAPII transcription in complex with cyclin H	(26)
CDK8	SMSACRE	C	Yes	G1 & G2 Phase of cell cycle RNAP II transcription in complex with Cyclin C, Wnt/β-catenin pathway in complex with cyclin C, Inhibition of lipogenesis in complex with cyclin C	(29, 31)
CDK9	PITALRE	T1 T2a T2b K	Yes	RNAPII transcription in complex with Cyclin T, DNA damage response in complex with cyclin K cdk9-cyclin k in maintaining genome integrity	(33, 34)
CDK10	PISSLRE	M	Yes	G2/M Phase Ets2 transcription	(36, 38)
CDK11	PITSLRE	L	Yes	G2/M Phase RNA splicing in complex with cyclin L	(43-45)
CDK12	PITAIRE	K/L	Yes	RNAPII transcription in complex with cyclin K DNA damage response in complex with cyclin K	(7, 53, 56)
CDK13	PITAIRE	K/L	Yes	RNAPII transcription in complex with cyclin K	(7, 53, 56)

Continued Table 1.

Protein	Cyclin binding element	Cyclin	Kinase Activity	Cellular Function	References
CDK14	PITAIRE	Y	Yes	Wnt/ β-catenin pathway in complex with cyclin Y	(61, 62)
CDK15	PITAIRE	Y	Yes	Synaptic trafficking and remodeling in complex with cyclin Y	(70, 71)
CDK16	PCTAIRE	Y	Yes	PCTAIRE proteins or PCTK1/ displays kinase activity during S phase and the G2 phase/ Spermatogenesis in complex with Cyclin Y	(66, 69, 73)
CDK17	PCTAIRE	Y	Yes	PCTAIRE proteins or PCTK2/ iSer/Thr kinase that might play a unique role in terminally differentiated neurons.	(72)
CDK18	PCTAIRE	K	Yes	post-mitotic Function PCTAIRE proteins or PCTK3/ phosphorylates TAU protein regulator of genome integrity	(60, 74, 76)
CDK19	SMSACRE	C		Associated with C-type cyclins as part of the multi-subunit Mediator complex Links to transcription factors with Pol II	(60, 74, 76, 77, 79)
CDK20	PNQALRE	H	Yes	CAK (CDK-activating kinase) activity for Cdk2, activating kinase for MAK-related kinase/intestinal cell kinase (ICK) activates β-catenin-TCF signaling to stimulate cell-cycle progression	(81, 82)

autophagy [46-48]. Various studies have demonstrated that Cdk11, is specifically expressed at G2-M, (Figure 1) and during mitosis its kinase activity is required for duplication of the ntrioles, spindle dynamics and sister chromatid cohesion at centromeres [44,49-50].

The Cdk12 and Cdk13, both paired with cyclin K and identified in cDNA screens for cell cycle regulators. They were initially named CRKRS and CDC2L5 [51] and play role in regulation of transcription through the differential phosphorylation of the C-terminal domain (CTD) of RNA Polymerase II [7-52-53].

CDK12 (alias CRKRS, CRK7, CRKR, KIAA0904) was originally identified as a Cdc2-related serine/threonine kinase (STK) possessing an arginine/serine (RS)-rich domain, which was closely related to the family of CDKs. [52-54]. Previously Chen and his group have reported its interaction with cyclins L1 and L2 (CycL) [55], however various studies have now identified cyclin K (CycK), as the endogenous binding CDK12 partner [53-56].

Ko et al. proposed that CDK12 could play a role in the regulation of transcription and alternative splicing rather than cell cycle progression [51]. They have hypothesized that CDK12 could be a novel RNA polymerase II (RNAPII) kinase that might directly link transcription with the splicing machinery. Previously Rodrigues et al. proposed that CDK 12 acts a splicing regulator (Figure 5a) for glial-specific splicing of NeurexinIV on specific pre-mRNA sites defined by HOW (sequence specific RNA binding protein) [57]. CDK12 has also shown an indirect role in the cellular process of DNA damage response (DDR) and maintenance of genomic stability by modulating the expression of DDR genes. The authors also demonstrated that CycK/CDK12 depletion increases the number of cells in the G2-M phase of the cell cycle [53].

CDK13 protein kinase is also involved in the regulation of gene expression by controlling the phosphorylation status and activity of splicing regulators [54-58]. It is part of a family of 20 different ATP-dependent serine-threonine protein kinases regulating cell-cycle progression and gene expression [6]. It is known to interact with two types of regulatory subunits, K and L-type cyclins [53-55]. In addition, CDK13 interacts with p32 a protein associating with the splicing factor SRSF1 (also known as ASF/SF2) and by phosphorylating SRSF1 (Figure 5b), this complex increases the mRNA splicing of human immunodeficient virus type 1 (HIV-1) while its overexpression, suppresses virus production [59].

The activity of some CDKs requires protein motif PFTAIRE (Cdc2-related kinases) which mediates binding to co-activating proteins called cyclins and has been classify other newly identified CDKs including CDK14 (PFTK1), CDK15 (PFTK2), CDK16 (PCTK1), CDK17 (PCTK2) and CDK18 (PCTK3) or on a sequence homology with the CDKs, such as CDC2-like kinase (CDK19) or cell cycle-related kinase (CDK20) [60]. Previously it was reported that CDK14 associated with cyclin Y and exert their influence over Wnt signal transduction (Figure 5 c) remotely at the cell surface which are anchored to the plasma membrane [61-62]. Furthermore, CDk14 over expression has been found in various human cancers [63-65].

The PFTK2/CDK15 is very poorly characterized kinases, and little is known about its expression and regulation. Evolutionarily, CDK15 seems to be of a newer origin, which is more similar to CDK14 (PFTK1). A Previous study found that PCTK-1/CDK16 is present in

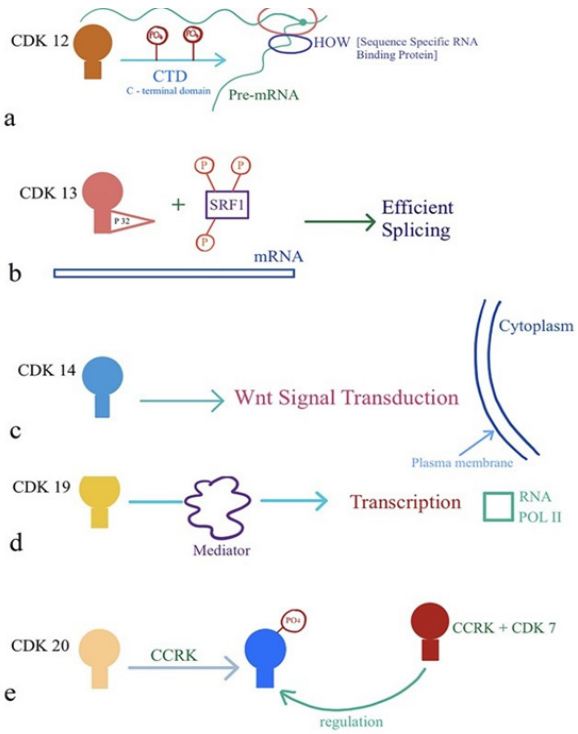

Figure 5. Biological role of CDKs (a) CDK12, (b) CDK13, (c) CDK14, (d) CDK19, (e) CDK20

the cytoplasm throughout the cell cycle and displays kinase activity during S phase and the G2 phase (Figure 1) and correlated with dephosphorylation of tyrosine residues. [66]. Abundant expression of Cdk16 was also detected in post-mitotic brain cells [67] and subsequently, high levels of CDK16 are found in the cytoplasm of cerebellar Purkinje cells, as well as in cells of the hippocampus and the neocortex [68]. In mammals, CDK16 is required for spermatogenesis, [69] polarization of presynaptic vesicles and synapse elimination during neural circuit rewiring in nematodes [70-71].

Hirose T et al and his group found transcripts of rat PCTK2/CDK17 in the hippocampal and olfactory bulb regions of the brain [72]. It was also shown to interact with TRAP (Tudor repeat associated with PCTK2)16 as well as cables (adaptor molecule linking the non-receptor tyrosine kinase c-abl with CDKs) [73].

PCTAIRE kinase 3 (PCTK3) or CDK18 was first reported in human Alzheimer's brain as neuronal kinase that phosphorylates TAU protein [74]. Previous study showed the mechanisms of catalytic activation of PCTK3 by cyclin A2 and protein kinase [75]. It was also showed that cdk18 has role in replication stress signaling and serves as a novel regulator of genome integrity [76].

The cdk19 (previously known as CDK8-like, CDK8L or CDC2L6) protein is similar to cdk8, although both CDK8 and CDK19 associate with C type cyclin as a part of the multi-subunit Mediator complexes [4,6-77-78] which links transcription factors with Pol II [79]. However, a recent study identified a novel links between CDK19 and cell proliferation, p53 response, and cholesterol metabolism [80]. Established and emerging functions of CDKs are summarized in Table 1.

Finally, Cdk20 (also known as cell cycle-related kinase (CCRK), is associated with cyclin H and known as an important regulator of G1- to S-phase transition in cell cycle while it has CDK activating kinase (CAK) activity for Cdk2, suggesting a close relationship with Cdk7 [81]. Expression of Cdk20 causes activation of β-catenin-TCF signaling which in turn to stimulate the cell-cycle progression [82], whereas CAK inhibition results in accumulation of intestinal cell kinases at the ciliary tips and prevents cell-cycle entry [65].

Thus far, CDKs family implicated in transcription, DNA damage repair, proteolytic degradation, epigenetic regulation, and metabolism, stem cell self-renewal, neuronal functions and spermatogenesis.

In conclusions, CDKs and multifaceted proteins cyclins are the essential regulators of the cell cycle and have a tremendous role in different biological processes that are distinct from cell division. However, the majority of these emerging functions are closely intertwined with the cell cycle.

Abbreviations

CDK: Cyclin dependent Kinases
CDC2: Cell division cycle 2
HESC: human embryonic stem cells
CTD: C Terminal Domain
TF1: Transcription factor 1
ATM: ataxia-telangiectasia mutated
CCRK: Cell cycle-related kinase
SKP2: S-phase kinase associated protein
Pol II: Polymerase II
P-TEF: Positive Transcription Elongation factor

Competing interests

The authors declare that they have no competing interests

Authors' contributions

SM designed the basic frame work and outline of manuscript, wrote and revised manuscript. MS, MFHQ, DM, ML and TU designed all the graphics, managed literature searches and provided help in manuscript preparation. All authors have read and agreed to the published version of manuscript.

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