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Review

Molecular basis for the regulation of the circadian clock kinases CK1δ and CK1ε

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ABSTRACT

CK1δ and CK1ε are unique in the casein kinase 1 family and play critical roles in a number of physiological intracellular pathways. In particular, these kinases are involved in composing the mammalian circadian clock by phosphorylating core clock proteins. Considering that CK1δ/ε phosphorylate other key biological molecules, such as β-catenin and p53, understanding how the kinase activity is regulated would be greatly significant, since they are potential targets to develop pharmacological agents against cancer, pain, and circadian disorders. In this review, we summarize current knowledge attributed to kinase regulation including expression regulation, post-translational regulation, and kinase activity modulation by small molecules. Finally, we discuss how the kinase activity is regulated from a structural point of view.

Contents

Abbreviations: ATP, adenosine triphosphate; CK1, casein kinase 1; CK2, casein kinase 2; CTD, C-terminal domain; TTFL, transcriptional and translational feedback loop; GSK-3β, glycogen synthase kinase 3β; MEFs, mouse embryonic fibroblast cells; ConA, concanavalin A; LPS, lipopolysaccharide; PKD2, protein kinase D2; mGluRs, metabotropic glutamate receptors; DHPG, (*S*)-3,5-dihydroxyphenylglycine; DARPP-32, dopamine and cAMP-regulated phosphoprotein; MAP1A, microtubule associated protein 1A; CLS, centrosome localization signal; CK1BP, casein kinase-1 binding protein; PKA, cAMP-dependent protein kinase; CDKs, cyclin dependent kinases; ChK1, checkpoint kinase 1; AMPK, AMP-activated protein kinase; CKI-7, N-(2-aminoethyl)-5-chloroisoquinoline-8- sulfonamide; IC261, 3-[(2,4,6-trimethoxyphenyl)-methylidenyl]-indolin-2-one; PF480, 3-(3-chloro-phenoxymethyl)-1-(tetrahydro-pyran-4-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-ylamine; PF670, 4-[3-cyclohexyl-5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-pyrimidin-2-ylamine; P-loop, phosphate-binding loop; DVL, dishevelled; FASPS, familial advanced sleep phase syndrome; DSPS, delayed sleep phase syndrome; N-24, non-24-hour sleep-wake syndrome.

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1. Introduction

Protein phosphorylation is known to be critical in regulating many important biological processes, and is catalyzed by kinases which transfer the γ-phosphate from ATP to the donor residues serine, threonine or tyrosine in proteins. The kinase superfamily in humans consists of over 500 members, which is about 2% of the human genome [1]. The casein kinase 1 (CK1) family, which has seven members (α, β, γ1, γ2, γ3, δ and ε) in mammals, belongs to the serine/threonine protein kinase family. All seven members share highly conserved sequences in their kinase domain, but the casein kinases 1δ (CK1δ, encoded by the *cskn1d* gene) and 1ε (CK1ε, encoded by the *cskn1e* gene) have the highest similarity in the C-terminal domain (CTD) that is not conserved in other CK1 isoforms. From a phylogenetic view, CK1δ and CK1ε occupy a small but very unique branch in the kinase family (Fig. 1). Reviews of the CK1 family are discussed elsewhere [2,3], so this article will focus only on CK1δ and CK1ε due to their high similarity and their essential roles in the circadian clock.

The first discovered mammalian clock mutant was the *tau* mutant in hamsters [4] which was genetically mapped to the *csnk1e* gene locus [5]. CK1δ and CK1ε are the key kinases in the signaling pathways that control the circadian clock [6,7]. Mammalian core clock proteins, Period 1 (PER1) and Period 2 (PER2), are phosphorylated by CK1δ and CK1ε and their phosphorylation controls their turnover rates through proteasome-mediated degradation, which then sets the speed of the clock [8–10]. Mouse embryonic fibroblast cells (MEFs) isolated from CK1δ deficient mice exhibited robust rhythmicity with a period approximately 1 h longer than wild type [6], while CK1ε knockout mice exhibited a small but significant period lengthening compared to the wild type [11]. Furthermore, disruption of CK1ε in the CK1δ deficient MEFs abolished the rhythms of Per2 abundance and phosphorylation, resulting in arrhythmicity [6]. Therefore, CK1δ and CK1ε have redundant roles in the circadian clock, though they function differently in other pathways as discussed in the following section. Hereafter, "CK1δ/ε" will be used in the text when their functions cannot be separated. Other core clock proteins, BMAL1 and CRYs, are also substrates for CK1δ/ε in the presence of PER proteins [12]. These clock proteins, plus CLOCK, constitute the core transcriptional and translational feedback loop (TTFL) that sets the clock to align with day/night phase. In this TTFL model, CK1δ/ε have been considered constitutively active kinases, but growing evidence appears to indicate that the CK1δ/ε kinases are modulated during physiological intracellular activities [13–15].

Beyond their roles in the circadian clock, CK1δ/ε act as important regulators of human health conditions such as somatic tumor formation, diabetes, neuro-degenerative diseases, and pain [3,16–18]. Activity modulation is a key to understanding the fundamental mechanism by which a kinase is involved in the pathways. How CK1δ/ε are modulated is not well understood at a molecular level and a few recent studies have looked into the issue. This article discusses certain aspects that have been studied to indirectly and/or directly modulate the kinase activities of CK1δ/ε, including the regulation of kinase expressions and the modulation of kinase activities. This article will conclude with a discussion of how the kinase activity is modulated by taking a structural point of view from known crystal structure features of CK1δ and CK1ε and the related biochemical studies. Some of the modulations may be strictly applied to the circadian clock pathway, but would also obviously apply to the roles that CK1δ/ε play in circadian syndromes or other cellular pathways. This review may be beneficial to understand the cross-talk between the circadian clock and other pathways, such as cell proliferation and the WNT signaling pathway.

2. Regulation of expression

2.1. Expression in various tissues

Like other proteins, the tissue specific expression of CK1δ/ε may be tightly regulated. Though no mechanism has been reported to play a role in the transcriptional regulation of the *cskn1d/e* genes, expression profiles of these two genes have been investigated in various tissues. The Mouse Brain Atlas shows that with *in situ* hybridization images, CK1δ expression is only detected in the area of hippocampal formation, while CK1ε expression is in all the brain areas, such as the isocortex, olfactory areas, hippocampal formation, hypothalamus, and thalamus [19]. Expression revealed by Northern blot shows that both genes are ubiquitously expressed in many human tissues, while CK1ε but not

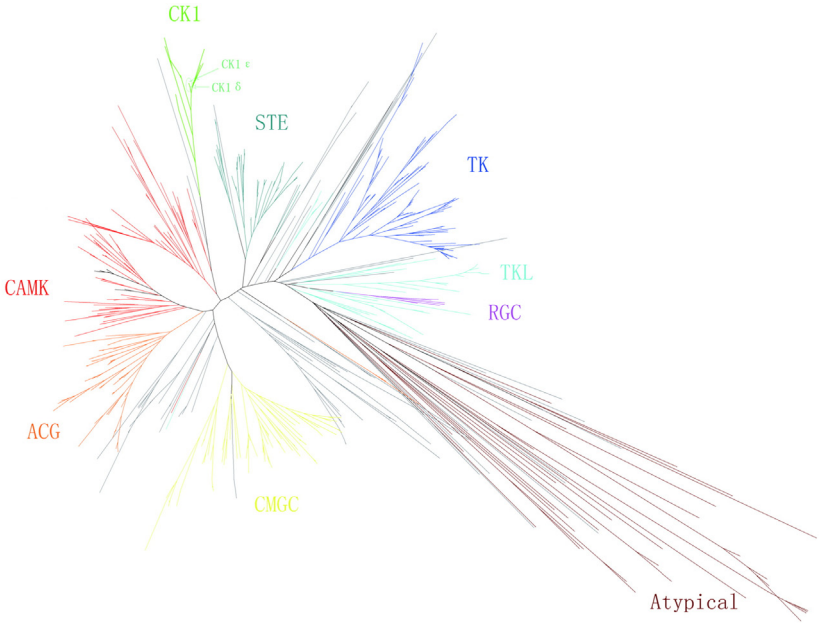

Fig. 1. Phylogenetic analysis of the human kinome of 547 kinases. Major groups are labeled and colored. CK1, casein kinase 1; STE, homologs of the yeast STE7, STE11 and STE20 genes; TK, tyrosine kinase; TKL, tyrosine kinase-like; RGC, receptor guanylate cyclases; CMGC, named after CDK, MAPK, GSK3 and CLK; ACG, protein kinase A, G, and C families; CAMK, calmodulin/calcium regulated kinases; atypical, without structural similarity. The protein sequences of these kinases were downloaded from the website **www.kinase.com**