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Review

CtIP, a candidate tumor susceptibility gene is a team player with luminaries

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Abstract

CtIP is a nuclear protein conserved among vertebrates that was discovered as a cofactor of the transcriptional corepressor CtBP. CtIP also interacts with the tumor suppressors such as BRCA1 and the pRb family members through binding sites that are frequently mutated in human cancers. CtIP is a target for BRCA1-dependent phosphorylation by the ATM kinase induced by DNA double strand breakage. CtIP plays a role in DNA-damage-induced cell cycle checkpoint control at the G2/M transition. Homozygous inactivation of the *Ctip* gene causes very early embryonic lethality during mouse development. The $Ctip^{-/-}$ embryo cells are arrested in G1 and do not enter S phase. Depletion of *Ctip* in established mouse embryo fibroblasts arrests cells in G1 and results in an accumulation of hypophosphorylated Rb and the Cdk inhibitor p21, suggesting that CtIP is also a critical regulator of G1/S transition of the cell cycle. The *Ctip* gene contains a mononucleotide (A9) repeat and one of the alleles is mutated at a high frequency in colon cancers with microsatellite instability. The $Ctip^{+/-}$ mice develop multiple types of tumors suggesting that haploid insufficiency of *Ctip* leads to tumorigenesis. Among the various tumor types observed in $Ctip^{+/-}$ heterozygous mice, large lymphomas are prevalent. Recent studies raise the possibility that *Ctip* may itself be a tumor susceptibility gene and suggest that it might be important for the activities of tumor suppressors BRCA1, pRb family proteins and Ikaros family members.

Keywords: *CtIP*; BRCA1; pRb; DNA repair

Contents

1. Introduction

CtIP (CtBP-interacting protein) was originally identified as an interacting partner of the transcriptional corepressor, CtBP [1]. These studies revealed that CtIP interacts with CtBP through a motif, PLDLS [2,3], which is highly conserved among viral and cellular CtBP-binding proteins [4] and the interaction between CtBP and CtIP was disrupted by the adenovirus E1A oncoprotein [1]. A high throughput yeast two hybrid screening of 1600 known protein targets against CtIP identified specific interaction of CtIP with pRb family members, pRb, p107 and p130 [5]. CtIP contains a sequence motif LECEE that is similar to the Rb-binding motif, LXCXE [6,7] which is important for interaction with pRb family

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members [5]. A conventional two hybrid screening also detected specific interaction between pRb members (pRb and p130) and CtIP [8]. A search for proteins that interact with the C-terminal (BRCT) domains of the breast cancer-associated tumor suppressor protein BRCA1 also identified CtIP [9–11]. Importantly, tumor-associated mutations within the BRCT domains of BRCA1 abolished its interaction with CtIP, highlighting the functional relevance of CtIP interaction for the tumor suppressive function of BRCA1. CtIP also complexes with members of the Ikaros family that encode Krüppel-like zinc finger transcription factors that regulate lymphoid development and differentiation [12]. Ikaros family members are also tumor suppressors in the lymphoid tissues and deregulated expression of these proteins is observed in human leukemias [13,14]. Association with three different established tumor suppressors suggests that CtIP might be an important player in tumor suppression in humans. Recent genetic studies with mice indicate that haploid deficiency in the *Ctip* gene may predispose mice for several types of tumors suggesting that *Ctip* itself might be a tumor suppressor gene. This review summarizes our current knowledge on CtIP.

2. CtIP protein

The human *Ctip* gene codes for an 897 amino acid nuclear protein [1,15] and is localized on chromosome 18q11.2 [5]. Although it is widely expressed in various human tissues, thymus and testis appear to express the highest levels [10]. The primary amino acid sequence of CtIP is significantly conserved among mammals. Avian and *Xenopus* homologs share a high degree of homology over the N-terminal and C-terminal regions, including a highly conserved CtBP binding motif (Fig. 1). Although the CtIP of some animal homologs do not contain a LXCXE motif, the possibility that they may interact with pRb independent of the LXCXE motif cannot be ruled out since hCtIP interacts with pRb in a LXCXE-dependent and an independent manner [16]. While the LXCXE motif may not be fully required for interaction with pRb, it may be essential for interaction with other Rb family members. The Rb-binding transcriptional regulatory protein RBP2 binds with pRb through a domain containing several charged amino acid residues while it binds to p107 through the LXCXE motif [17].

In mammalian cells, the pattern of *Ctip* expression is comparable to that of *Brca1* and *Rad51* [18,19] which are also highly expressed in tissues such as testis and thymus where DNA double strand breaks occur commonly. The primary amino acid sequence of CtIP is not overtly informative with regard to its function, although some computer aided searches indicate some resemblance to proteins involved in DNA repair. CtIP contains a high affinity CtBP-binding motif [1,3], a functional Rb-binding motif [5] and four potential nuclear

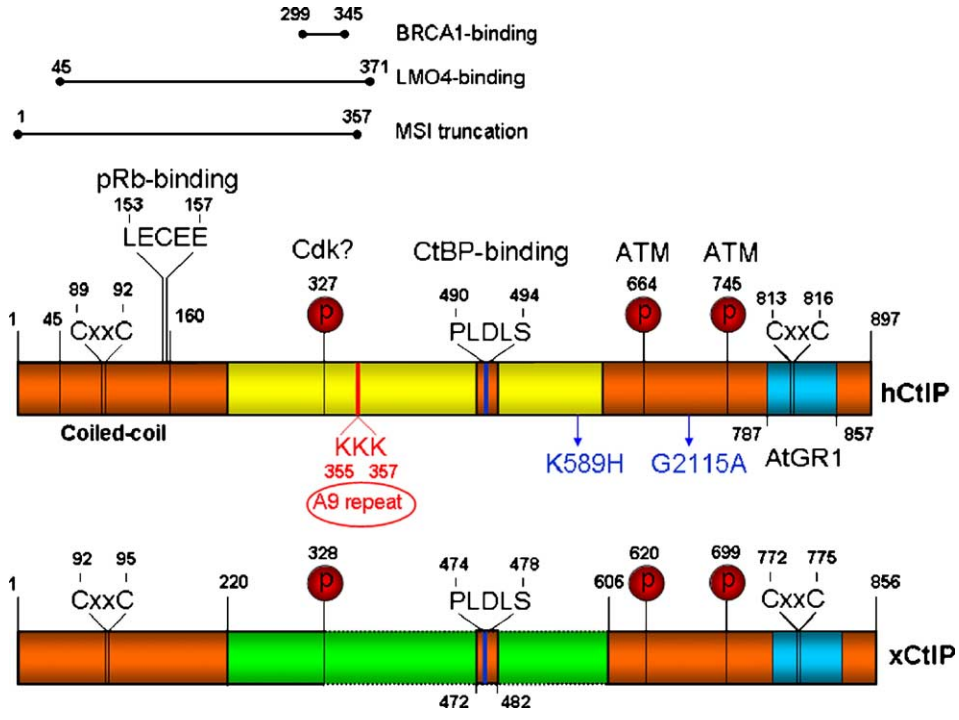

Fig. 1. Domain structure of hCtIP and xCtIP. All known CtIP proteins contain a highly conserved CtBP-binding motif, two CXXC motifs and a phosphorylation site that corresponds to Ser327 in hCtIP. The Rb-binding motif is conserved only in mammalian CtIP. The N-terminal and C-terminal regions of all the CtIP homologs show high degrees of conservation (indicated in xCtIP; N-terminal 220 and C-terminal 250 amino acid regions of xCtIP, orange color). The ATM target site that corresponds to Ser664 is not conserved in CtIP of certain species (e.g., mouse and chicken). The A9 repeat, a tumor-specific nucleotide polymorphism (G2115A) and a nucleotide polymorphism (G1766A) resulting in an amino acid substitution (K589H) observed in tumor and normal cells are indicated. The region between amino acid positions 45 to 160 (shown in hCtIP) is a coiled-coil. A C-terminal region conserved between CtIPs and the plant (*Arabidopsis thaliana*) gamma response 1 (AtGR1) protein is also indicated (light blue). hCtIP indicates human CtIP and xCtIP indicates *Xenopus* CtIP.