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Review

CIC (capicua transcriptional repressor)

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Abstract

CIC is a tissue-specific transcriptional repressor that is highly conserved between metazoan organisms and is required for the normal development of multiple adult structures. CIC functions to transduce receptor tyrosine kinase (RTK) signalling into gene expression changes through a mechanism termed default repression, wherein CIC is bound to target gene promoters or enhancers and inhibits transcription in the absence of signal.

This CIC-DNA interaction can be inhibited through activation of the RTK core signalling molecule mitogen-activated protein kinase (MAPK), which then allows for the transcription of CIC targets through this RTK-MAPK signalling axis. Components of RTK signalling are commonly dysregulated in cancers, possibly implying that CIC alterations observed in specific cancer types (e.g. oligodendroglioma and Ewing-like sarcomas) are a form of RTK signalling dysregulation that drives oncogenesis. CIC is also specifically expressed in cells of the developing central nervous system and its dysfunction is associated with the neurodegenerative disorder spinocerebellar ataxia type 1, implicating CIC in neuronal cell development and/or homeostasis. Other possible cellular and physiological roles for CIC include cell cycle control, ATP-citrate lyase phosphorylation, reactive oxygen species homeostasis, and bile acid homeostasis.

Keywords

Oligodendroglioma, spinocerebellar ataxia type 1, Ewing-like sarcoma, transcription factor, receptor tyrosine kinase

Identity

HGNC (Hugo): CIC

Location: 19q13.2

DNA/RNA

Description

CIC is located on the positive strand and spans approximately 27 kilobases. It has 21 exons. According to Entrez-Gene, CIC maps to NC_000019.10 of the assembly GRCh38.p2.

Transcription

There are two known isoforms of CIC: short (CIC-S) and long (CIC-L). CIC-S and CIC-L have alternative transcription start sites at exon 1 and exon 0, respectively, and share exons 2-20 (Figure 1).

Pseudogene

According to Entrez-Gene, CIC has 28 related pseudogenes.

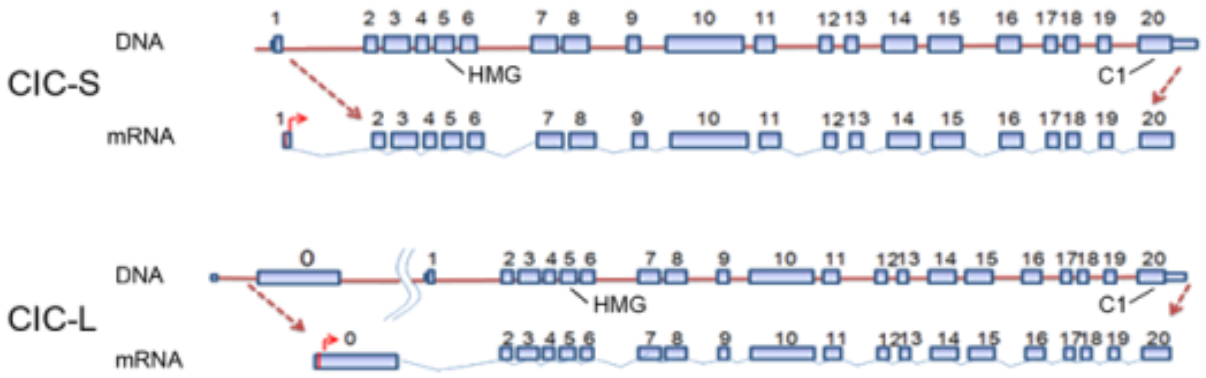

Figure 1. Exon structure of 2 main CIC isoforms in humans: CIC short (CIC-S) and long (CIC-L). The highly conserved DNA-binding high mobility group (HMG) box domain is encoded mostly by exon 5 and partially by exon 6 while the highly conserved C1 motif is encoded within exon 20. Figure was obtained from Chittaranjan et al. 2014 with labels added.

Protein

Expression

In Drosophila and zebrafish, CIC mRNA is maternally provided to the egg (Jimenez et al. 2000; Chen et al. 2014). In zebrafish and mice, CIC mRNA is detected at various developmental stages, especially in the developing central nervous system (Lee et al. 2002; Chen et al. 2014). In adult mice, CIC mRNA is relatively highly expressed in the brain, spleen, testis, and kidney. CIC mRNA may also be expressed in the heart, lung, mammary tissue, thymus, and lymph nodes in adult mice (Lee et al. 2002).

Localisation

CIC-S and CIC-L localize to both the cytoplasm and the nucleus in multiple human cell lines. CIC may also accumulate close to the mitochondria (Chittaranjan et al. 2014).

Function

CIC has invariably been observed to act as a repressor of transcription through its DNA-binding activity. CIC has a high mobility group (HMG) box domain that confers binding to an octameric DNA motif T(G/C)AATG(A/G)A within the promoters or enhancers of its target genes (Jimenez et al. 2012). In Drosophila, presence of this octameric motif at the regulatory region of a reporter gene was necessary to confer CIC-mediated transcriptional repression, although recruitment of a corepressor protein such as Groucho may be necessary to confer repression (Ajuria et al. 2011). CIC's DNA-binding activity can be inhibited through the activation (phosphorylation) of mitogen-activated protein kinase (MAPK), a core signaling molecule of receptor tyrosine kinase (RTK) pathways (Jimenez et al. 2002; Dissanayake et al. 2011). This provides a mechanism for allowing CIC target gene transcription upon RTK signaling. MAPK potentially regulates CIC's transcriptionally repressive activity in three ways: through direct binding with CIC (Astigarraga et al. 2007, Futran et al. 2015), through the activation of the downstream signaling molecule p90RSK (Figure 2) to inhibit CIC's DNA-binding activity (Dissanayake et al. 2011), or through influencing CIC's nucleocytoplasmic shuttling (Dissanayake et al. 2011, Grimm et al. 2012). CIC levels in turn also positively regulate MAPK phosphorylation in vivo in Drosophila by protecting MAPK from phosphatases (Kim et al. 2011).

CIC functions in multiple developmental contexts in both Drosophila and mammals. For example, in Drosophila, CIC can regulate proper embryonic patterning, cell differentiation to form wing vein cells, and cell proliferation in the developing eye. In all these contexts, CIC functions in cells by restricting the expression of specific target genes when an extracellular growth signaling molecule is absent (Jimenez et al. 2002; Roch et al. 2002; Tseng et al. 2007).

CIC has also been reported to function in reactive oxygen species homeostasis (Krivy et al. 2013), ATP-citrate lyase phosphorylation (Chittaranjan et al. 2014), and bile acid homeostasis (Kim et al. 2015).

Homology

CIC has homologs in mice, zebrafish, Drosophila, and C. elegans (Jimenez et al. 2000; Lee et al. 2002). Amino acid sequence identity of CIC's N1 domain, HMG box domain, and C1 motif (Figure 2) is highly conserved between species (Jimenez et al 2012). This indicates that at least some of CIC's biochemical functions are evolutionary conserved between animals.

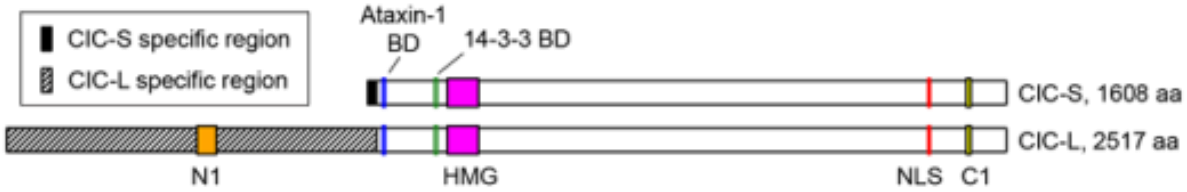

Figure 2. Functional domains of CIC short (CIC-S) and long (CIC-L) isoforms in humans. **N1:** Conserved CIC-L N-terminal domain of unknown function. **Ataxin-1 BD:** Binding domain that directly interacts with Ataxin-1 (Lam et al. 2006; Kim et al. 2013). **14-3-3 BD:** binding domain that directly interacts with 14-3-3 proteins. This domain harbours a serine residue that is phosphorylated by p90RSK to mediate 14-3-3 binding and consequent inhibition of DNA binding upon MAPK activation. An additional 14-3-3 BD flanking the other end of the HMG domain may also be required for 14-3-3 dimer recognition (Dissanayake et al. 2011). **HMG:** DNA-binding high mobility group box domain (Jimenez et al. 2000; Lee et al. 2002). **NLS:** Nuclear localisation signal recognized by the nuclear importer KPNA3. Phosphorylation of two nearby serine residues may mask the NLS and potentially interferes with nuclear shuttling upon MAPK activation. Other NLS sequence(s) may be encoded within the HMG domain (Dissanayake et al. 2011). **C1:** Highly conserved c-terminal motif that may be essential for CIC-mediated transcriptional repression in some contexts (Astigarraga et al. 2007). **C2:** Motif that mediates direct binding with MAPK (Futran et al. 2015).

Implicated in

CIC-rearranged Ewing-like sarcomas

The overwhelming majority of Ewing sarcoma/primitive neuroectodermal family of tumours (EFTs) harbour rearrangements of the EWSR1 gene with an ETS family member (Delattre et al. 1994; Mariño-Enrèquez & Fletcher 2014). However, up to 2/3 of EWSR1 fusion-negative EFTs may harbour rearrangements of CIC with a copy of DUX4 on either 4q35 or 10q26. CIC-DUX4. EFTs are aggressive and typically share characteristics such as geographical necrosis and greater heterogeneity in nuclear shape and size than classical EFTs (Italiano et al. 2012). CIC-DUX4 proteins have oncogenic transforming potential in vitro and may drive oncogenesis by strongly activating transcription of CIC's oncogenic target genes ETV1, ETV4, and ETV5 instead of normally repressing them (Kawamura-Saito et al. 2006). Consistent with this, EWSR1-ETV1 and EWSR1-ETV4 fusions, which presumably function as aberrant versions of the transcription factors ETV1 and ETV4, respectively, have been observed in EFTs (Jeon et al. 1995; Kaneko et al. 1996).

EFTs with CIC-FOXO4 fusions have also been reported (Sugita et al. 2014; Solomon et al. 2014).

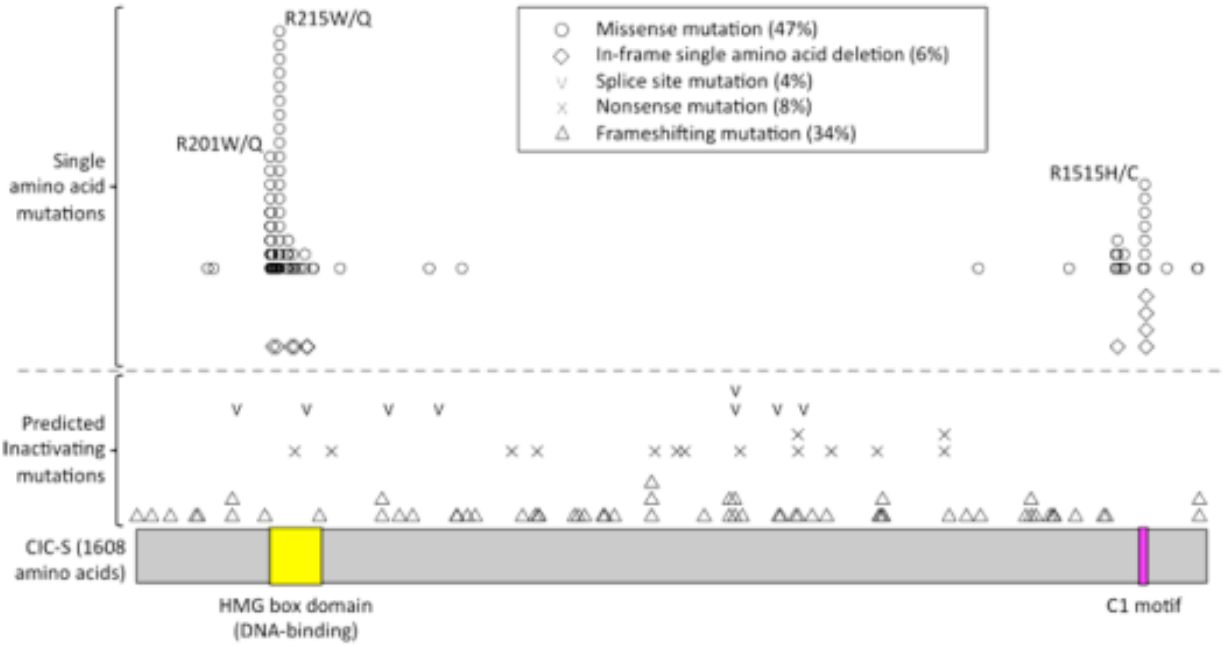

Figure 3. CIC-S: short isoform of CIC. HMG: high-mobility group. C1 motif: highly conserved c-terminal domain. Recurrently detected mutations are indicated in stacked symbols. Frequencies of different mutation types are given in parentheses. Mutational data were gathered from multiple sources (Bettegowda et al. 2011; Jiao et al. 2012; Sahm et al. 2012; Yip et al. 2012) and the cbioportal database (Gao et al. 2013; Chan et al. 2014). The results shown here are in part based upon data generated by the TCGA Research Network: http://cancergenome.nih.gov/.

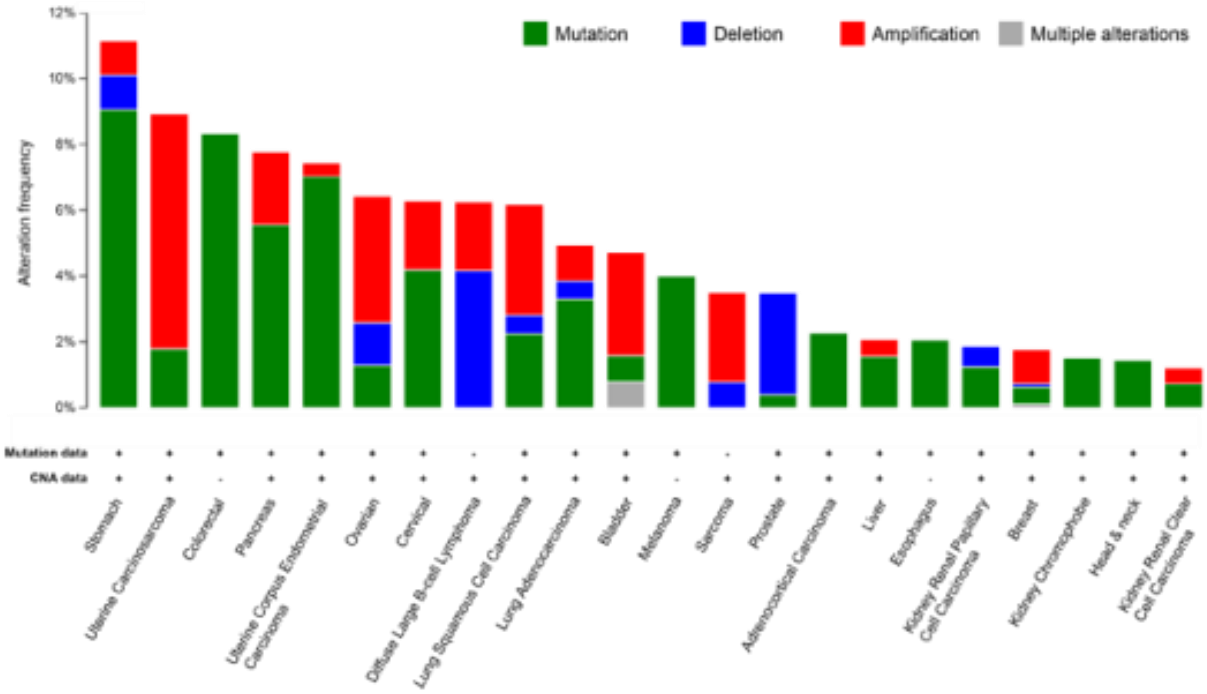

Figure 4. Frequency of CIC alterations detected in non-glioma cancers. Figure was obtained and modified from the cbioportal database (Cerami et al. 2012; Gao et al. 2013). The results shown here are in whole or part based upon data generated by the TCGA Research Network: http://cancergenome.nih.gov/. Cancer types with 2 or more detected CIC alterations are shown. CNA: copy number alteration.

Oligodendroglioma

CIC mutations are detected in about 70% of "classical" oligodendrogliomas (ODGs, i.e. gliomas harbouring deletions of the chromosomal arms 1p and 19q) (Bettegowda et al. 2011; Yip et al. 2012). Classical ODGs also present with a characteristic set of other somatic mutations, namely in IDH1 or IDH2 (in 100% of cases), in the TERT promoter (about 90% of cases), and in FUBP1 (about 25-40% of cases) (Bettegowda et al. 2011; Sahm et al. 2012; Jiao et al. 2012; Labussire et al. 2014). This indicates potential synergistic interactions between these mutations to promote ODG progression. Different types of detected CIC mutations seem to converge on conferring a CIC loss-of-function phenotype, indicating CIC mutations may inactivate a tumour suppressive activity (Gleize et al. 2015). A CIC mutation in a 1p/19q co-deleted background may also be compatible with the notion of a tumour suppressive role for CIC, since one allele is lost as a consequence of 19q loss while the other allele is mutated. However, there is an enrichment of CIC mutations that affect a single amino acid residue and may preserve CIC's structure (Figure 3). Such "hotspots" are often detected in oncogenes (Liu et al. 2011; Stehr et al. 2011). Multiple distinct CIC mutations can arise within different areas of a single ODG lesion (Suzuki et al. 2015), possibly implicating the importance of CIC mutations in driving clonal expansion but not necessarily tumour initiation.

Other cancers

Recurrent somatic CIC mutations, deletions, and amplifications have been detected in a number of other cancer types (Figure 4). Loss of CIC expression is also implicated in prostate cancer progression (Choi et al. 2015). CIC alterations may therefore promote oncogenesis in various cancers.

Spinocerebellar ataxia type 1

Spinocerebellar ataxia type 1 (SCA1) is an inherited neurodegenerative disorder that is caused by the production of a toxic form of the Ataxin-1 protein harbouring an expanded tract of glutamine residues (polyQ Ataxin-1) (Orr et al. 1993).

SCA1 pathogenesis is associated with a direct physical interaction of polyQ Ataxin-1 with CIC in a large (about 1.8 MDa) complex, as well as with a decrease in wild type Ataxin-1-CIC complex formation.

Modulation of CIC's transcriptionally repressive activity by polyQ Ataxin-1 provides a possible mechanistic basis for SCA1 pathogenesis (Lam et al. 2006; Bowman et al. 2007). SCA1 pathogenesis may also result from the preferential accumulation of another polyQ Ataxin-1 complex that includes the RBM17 protein and excludes CIC (Lim et al. 2008). In a mouse model of SCA1, a modest exercise regimen extends longevity by reducing CIC levels in the brainstem. CIC loss through genetic perturbation also mitigates multiple SCA1 phenotypes in this model (Fryer et al. 2011).

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