Regulation and function of capicua in mammals

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Abstract
Capicua (CIC) is an evolutionarily conserved transcription factor. CIC contains a high-mobility group (HMG) box that recognizes specific DNA sequences to regulate the expression of various target genes. CIC was originally identified in Drosophila melanogaster as a transcriptional repressor that suppresses the receptor tyrosine kinase signaling pathway. This molecule controls normal organ growth and tissue patterning as well as embryogenesis in Drosophila. Recent studies have also demonstrated its extensive functions in mammals. For example, CIC regulates several developmental and physiological processes, including lung development, abdominal wall closure during embryogenesis, brain development and function, neural stem cell homeostasis, T cell differentiation, and enterohepatic circulation of bile acids. CIC is also associated with the progression of various types of cancer and neurodegeneration in spinocerebellar ataxia type-1, systemic autoimmunity, and liver injury. In this review, I provide a broad overview of our current understanding of the regulation and functions of CIC in mammals and discuss future research directions.

Introduction
In 2000, the capicua (cic) gene was first identified in Drosophila melanogaster as a transcriptional repressor involved in the regulation of embryogenesis. Casanova and colleagues performed a P-element screen to identify genes required for anteroposterior patterning in Drosophila. These researchers found that a mutant embryonic phenotype characterized by a lack of abdominal segmentation but maintenance of head and tail structures was caused by a mutation in capicua (thus explaining the gene name, derived from the Catalan term meaning “head-and-tail”). Cic is required for organ growth and tissue patterning as well as anteroposterior and dorsoventral formation during embryogenesis in Drosophila. Cic represses the expression of genes downstream of receptor tyrosine kinases (RTKs), including Torso and epidermal growth factor receptor (EGFR). Therefore, Cic functions as a negative regulator of the RTK signaling pathway. Moreover, RTK signaling activation promotes the degradation and/or cytoplasmic translocation of Cic via phosphorylation, thereby inducing the expression of Cic target genes downstream of RTK pathways.

CIC is evolutionarily conserved from Caenorhabditis elegans to humans. CIC exists as two isoforms, the short form (CIC-S) and the long form (CIC-L), which differ at their N-termini (Fig. 1a). CIC harbors two conserved domains, the high mobility group (HMG)-box and C1 domain (Fig. 1a), which cooperatively recognize specific octamer DNA sequences. In mammals, CIC interacts with ataxin-1 (ATXN1), of which the polyglutamine (polyQ)-expanded form causes spinocerebellar ataxia type-1 (SCA1), a neurodegenerative disease. CIC contributes to the pathogenesis of SCA1 in mice via interactions with mutant ATXN1. A fusion between Cic and a transcription activator domain of double homeobox 4 (DUX4) (CIC–DUX4 fusion protein) was identified in Ewing-like sarcoma cells. CIC–DUX4 fusion proteins activate the expression of ETV1, ETV4, and ETV5, which encode oncogenic transcription factors, thereby promoting cancer progression. Many studies have verified that Cic functions as a tumor suppressor in various types of cancer. Endogenous functions of Cic have been elucidated by examinations of the phenotypes of Cic mutant mice. Cic deficiency results in defects in lung development, bile acid homeostasis, abdominal wall closure during embryogenesis, neuronal cell differentiation, brain development, and T cell subset differentiation. In this review, I focus on the...
roles of CIC in mammals; in particular, I summarize recent studies of (1) its functions in diseases, including neurological diseases and cancer, (2) its functions in development, and (3) its underlying regulatory mechanisms in mammalian cells.

**CIC functions in diseases**

**Spinocerebellar ataxia type-1 (SCA1)**

SCA1 is one of nine polyQ disorders. Expansion of the CAG repeat in ATXN1 results in a long polyQ tract-containing mutant ATXN1, which is associated with cerebellar neurodegeneration primarily due to Purkinje cell death. Phosphorylation at the S776 residue of ATXN1 is critical for the neurotoxicity of the polyQ-expanded ATXN1. CIC binds with a high affinity to ATXN1 in human cells. The CIC–ATXN1 complex is approximately 1.8 MDa in size, irrespective of the polyQ expansion in ATXN1. The S776A mutation reduces the incorporation of ATXN1 into large CIC–ATXN1 complexes, implying that the interaction with CIC contributes to the neurotoxicity of the polyQ-expanded ATXN1. Fryer et al. experimentally proved that CIC facilitates the pathogenesis of SCA1 using a Cic-deficient SCA1 mouse model (Atxn1<sup>154Q</sup>; Cic<sup>−/−</sup>) generated by crossing 154Q knock-in SCA1 (Atxn1<sup>154Q</sup>) mice with Cic hypomorphic (Cic<sup>−/−</sup>) mice<sup>15</sup>. A partial loss of CIC expression substantially attenuated the pathological and behavioral abnormalities of the Atxn1<sup>154Q</sup> mice<sup>15</sup>. Furthermore, the expression levels of some CIC target genes were downregulated in the cerebellum of the Atxn1<sup>154Q</sup> mice and were significantly rescued in the cerebellum of the Atxn1<sup>154Q</sup>; Cic<sup>−/−</sup> mice<sup>15</sup>. These findings suggest that the polyQ-expanded ATXN1 could enhance the transcriptional repressor activity of CIC for a subset of target genes, thereby contributing to the progression of SCA1. Disruption of the interaction between the polyQ-expanded ATXN1 and CIC inhibited the SCA1 disease phenotypes in mice, suggesting that SCA1 is caused by neurotoxicity driven by a gain-of-function of the polyQ-expanded ATXN1–CIC complex<sup>16</sup>.

**Cancer**

The first evidence for an association between CIC and cancer progression was the identification of the fusion between CIC and DUX4 as a result of a recurrent chromosomal translocation t(4;19)(q35;q13) in Ewing-like...
sarcomas. The CIC–DUX4 chimaeras are composed of the majority of the CIC protein, except for a small portion of the C-terminus, and the C-terminal region of DUX4 involved in transcriptional activation. The CIC–DUX4 fusion protein acquires transforming activity against NIH3T3 fibroblasts, indicating that CIC–DUX4 acts as a dominant oncoene. The chimeric proteins transcriptionally activate the expression of CIC target genes, including PEA3 group genes that encode the oncogenic transcription factors ETV1, ETV4, and ETV5. Several other studies have identified various additional chromosomal translocations generating CIC–DUX4 chimeric transcripts in round cell sarcoma as well as Ewing sarcomas via distinct regulatory programs. These proteins drive tumorigenesis and metastasis in sarcomas by transcriptionally activating the expression of CIC target genes, thereby promoting tumor growth and metastasis via derepression of ETV4, ETV5, and SOX2 in breast cancer. CIC levels are substantially downregulated in hepatocellular carcinoma (HCC), glioblastoma (GBM), and colorectal cancer (CRC). The decreased expression of CIC leads to the derepression of PEA3 group genes, thereby promoting cell growth and invasion in PC, HCC, GBM, and CRC cell lines. Notably, the major PEA3 group members (e.g., ETV1, ETV4, or ETV5) regulated by CIC differ among cancer cell types; the expression of ETV5 and ETV4 is highly and significantly upregulated by CIC deficiency in PC and HCC cell lines, respectively. CIC is also involved in the control of cancer stem cell properties. CIC deficiency promotes the self-renewal capacity and increases the expression of cancer stem cell markers, including EpCAM+/CD44+/CD24− and ALDH4+, via derepression of ETV4, ETV5, and SOX2 in breast cancer cell lines. Consistent with this result, CIC levels were decreased in breast cancer patient samples with a CD44 high and CD24 low phenotype. These data suggest that CIC suppresses breast cancer formation by restricting cancer stemness and identify CIC as a potential regulator of stem cell maintenance.

**Functions of CIC in development**

**Lung development**

Defective lung alveolarization has been observed in Cic−L−/− mice, in which Cic-L expression is completely abolished and Cic-S expression is substantially reduced but incompletely blocked. Cic−L−/− mice exhibited perinatal lethality; approximately 83% of Cic−L−/− mice died before postnatal day 14 (P14; unpublished data), and the survivors were smaller than the wild-type (WT) littermates. Cic−L−/− survivors had lung alveolarization defects causing air space enlargement accompanied by MMP9 overexpression in the lungs at P20. Another germline Cic mutant (Cic−/−) mouse with deletions in Cic exons 2–6 (i.e., the HMG box-encoding exons), which expresses mutant Cic-L and Cic-S isoforms that lack the HMG box in the whole body, also exhibited defects in the terminal differentiation of the respiratory epithelium at embryonic day 18.5 (E18.5), potentially leading to delayed or altered alveolar maturation during postnatal development. The Cic levels were relatively high in the lungs of E18.5 embryos.

**Abdominal wall closure**

Characterization of Cic−2/−/− mice revealed that Cic is required for late embryonic development. Homozygous
Cic^{−/−} embryos were present in Mendelian ratios at E18.5 but died immediately after birth. Approximately 70% of the E18.5 Cic^{−/−} embryos had an omphalocele, a mild type of abdominal wall closure defect. In this case, the gut protrudes into the umbilical ring in the late embryonic stage. Therefore, one explanation for the early death of Cic mutant mice is that a part of the internal organs, such as the intestines, is cannibalized when the mother removes the placenta after birth. The abdominal wall closure defect was also found in mice that lack the expression of ATXN1 and ATXN1-like (ATNX1L), which bind to and stabilize Cic. Approximately 45% of the E18.5 Atxn1 and Atxn1l double null embryos had an omphalocele. Taken together, these findings suggest that the Cic-ATXN1/ATXN1L complex is essential for normal embryogenesis and viability.

**Brain development and function**

Cic is highly expressed in the brain. This molecule has been implicated in granule cell development based on the observation that Cic is highly expressed in immature granule cells in the cerebellum, hippocampus, and olfactory bulb. A study of Cic mutant mice uncovered a critical role of Cic in brain development and function. The deletion of Cic in the forebrain significantly reduced the thickness of cortical layers 2–4 and the dentate gyrus, potentially due to defects in the maintenance of postmitotic neurons. The layer 2/3 pyramidal neurons of the forebrain-specific Cic null (Cic^{−/−};Emx1-Cre) mice also had defective dendritic branching. Cic deficiency in the forebrain caused learning and memory deficits, and a loss of Cic in the hypothalamus and medial amygdala led to defects in social interactions. Consistent with these mouse data, de novo heterozygous truncating mutations in Cic are associated with autism spectrum disorder, developmental delay/intellectual disability, seizures, and attention deficit hyperactivity disorder in humans.

Cic is also associated with NSC maintenance and differentiation. Cic null NSCs presented EGF-independent hyperproliferative characteristics. Hyperproliferation of NSCs by the loss of Cic was also confirmed in E13 embryos by a 5-ethynyl-2′-deoxyuridine (EdU) labeling experiment. Upon the induction of differentiation in vitro, Cic null NSCs could not differentiate into mature oligodendrocytes and instead were maintained in an oligodendrocyte progenitor cell (OPC)-like stemness state. A similar result was obtained using another forebrain-specific Cic null (Cic^{−/−};Foxg1-Cre) mouse model, in which Olig2^{+/−}Sox2^{+} cells and Olig2^{−/−}Pdgfra^{+} OPCs are increased and CNPase^{−/−} immature oligodendrocytes are decreased in the cortex. Moreover, Cic deficiency enhanced the self-renewal capacity and promoted the symmetric division of NSCs. Mechanistically, the derepression of Etv5 mediated the effects of Cic deficiency in NSCs. Thus, Cic is a key transcription factor that controls brain development and function as well as the pathogenesis of neurological disorders.

**Immune cell development and function**

Park et al. investigated the role of Cic in the immune system by generating and characterizing hematopoietic lineage cell-specific Cic null (Cic^{−/−};Vav1-Cre) mice. These mice had lymphoproliferative disorder-like symptoms at 9 weeks of age, as evidenced by an increased splenocyte count mainly due to the expansion of the B220^{+} B cell population and hyperglobulinemia. Cic^{−/−}; Vav1-Cre mice eventually developed systemic autoimmune-like phenotypes, including the enlargement of secondary lymphoid organs; increased anti-dsDNA antibody serum levels; immune cell infiltration into various organs, including the liver, lung, and kidney; and IgG deposition at the glomeruli of the kidney. T cell-specific Cic null (Cic^{−/−};Cd4-Cre) mice also exhibited similar phenotypes to Cic^{−/−}; Vav1-Cre mice, suggesting that Cic deficiency in T cells is critical for the induction of autoimmune-like symptoms. Cic deficiency promotes the differentiation of follicular helper T (Tfh) cells, which play a pivotal role in the germinal center reaction to produce isotype class switched high affinity antibodies against specific antigens. At the molecular level, Etv5 is a critical target gene of Cic for the regulation of Tfh cell differentiation. ET5V levels were significantly upregulated in Cic null Tfh cells compared with WT cells. Adaptive transfer experiments using OT-II cells, ovalbumin-specific T cell receptor-expressing CD4^{+} T cells, revealed that ET5V overexpression promotes Tfh cell development and that the knockdown of ET5V substantially rescues the enhanced Tfh cell differentiation of Cic null OT-II cells. These results indicate that the Cic-ET5V axis controls Tfh cell development. Park et al. also proposed that Maf, which encodes a transcription factor that promotes Tfh cell differentiation, is a target of ET5V in CD4^{+} T cells under STAT3 activation.

Cic is also involved in maintaining homeostasis of bone marrow hematopoietic stem and progenitor cells (HSPCs) and early T cell development. Analyses of bone marrow and thymic cells in adult stage-specific (Cic^{−/−};UBC-Cre/ERT2) and endothelial and hematopoietic lineage cell-specific (Cic^{−/−};Tek-Cre) Cic null mice have shown that the number of HSPCs, including hematopoietic stem cells (HSCs) and multipotent progenitors (MPPs), is reduced, whereas the frequency of thymic double negative 1 (DN1) cells is significantly increased. The frequency of early T cell precursors (ETPs), a subset of DN1 cells from the bone marrow that remain pluripotent, is also elevated in the thymus of Cic^{−/−};UBC-Cre/ERT2 mice, suggesting that...
CIC regulates the self-renewal capacity of stem-like cells.

CIC has been implicated in the development of CD8+ resident memory T (Trm) cells in the liver. Cic−/− mice exhibit liver damage, as evidenced by increases in serum alanine transaminase (ALT) and hepatic proinflammatory cytokine expression levels. These mice also have defects in the enterohepatic circulation of bile acids accompanied by the downregulation of several key genes involved in bile acid biosynthesis and transport in the liver. These liver dysfunctions are not due to a CIC deficiency in hepatocytes because liver-specific Cic null (Cicfl/fl;Alb-Cre) mice do not recapitulate these phenotypes. Cicfl/fl;Cd4-Cre mice have increased serum ALT and hepatic proinflammatory cytokine expression levels, indicating that CIC-deficient T cells cause inflammatory liver injury. Cic deficiency promotes the formation of liver CD8+ Trm-like cells expressing surface markers, such as CD69+, CD49a+, CXCR6+, CXCR3+, and CD103+, in a cell intrinsic manner. Moreover, the suppression of liver CD8+ Trm-like cell formation dramatically mitigated liver injury phenotypes in Cicfl/fl;Cd4-Cre mice treated with acetaminophen, which induces acute liver injury, suggesting that the increased CD8+ Trm-like cell population in the liver is responsible for the CIC deficiency-induced liver injury. Mechanistically, the CIC–ETV5 axis controls liver CD8+ Trm-like cell differentiation. The derepression of ETV5 induces the expression of HOBIT, a transcription factor required for Trm cell development, in Cic null CD8+ T cells, thereby promoting Trm cell differentiation.

Regulation of CIC

RTK-RAS-MAPK pathways suppress CIC activity via the cytoplasmic translocation and/or degradation of CIC (Fig. 1b). This regulatory mechanism was originally discovered in studies of CIC expression patterns in Drosophila embryos. Torso RTK signaling in the early embryo leads to the degradation of CIC, whereas EGFR signaling in the ovarian follicle induces the partial relocalization of CIC to the cytoplasm. EGFR treatment resulted in the phosphorylation of human CIC-S at 20 different serine/threonine residues, presumably by ERK and p90RSK, a kinase activated by ERK. In particular, p90RSK-mediated phosphorylation of S173 is critical for 14–3–3 binding (Fig. 1a), which inhibits CIC binding to target DNA sequences. S1409 phosphorylation prevents the binding of importin α4/KPNA3 to the nuclear localization signal of CIC. However, the disruption of the CIC-KPNA3 interaction does not affect the nuclear localization of CIC-S, suggesting that other transport-related factors might be required for the cytoplasmic translocation of CIC in mammalian cells. ERK binds to the C-terminal region of human CIC-S containing residues 1335–1359 (prior to the C1 domain; Fig. 1a). EGFR stimulation decreased CIC levels in mammalian cells. The inhibition of ERK by treatment with MEK1/2 inhibitors increased the levels of nuclear CIC-S at the expense of cytoplasmic CIC expression in pancreatic cancer cells, suggesting that ERK regulates the subcellular localization of CIC (Fig. 1b). Moreover, EGFR-activated c-Src tyrosine kinase mediates cytoplasmic translocation of CIC-S via phosphorylation of the Y1455 residue (Fig. 1a, b). DNA binding of CIC is a prerequisite for the PJA1-mediated polyubiquitylation of CIC. In addition, PJA1 recognizes the S173 residue of CIC-S to interact with CIC. Since 14–3–3 also binds to S173-phosphorylated CIC-S to control the transcriptional repressor activity of CIC, crosstalk between 14–3–3 and PJA1 might be involved in the regulation of CIC activity and/or stability.

Another regulatory mechanism underlying CIC activity is the ATXN1/ATXN1L interaction-mediated stabilization of CIC (Fig. 1b). Both ATXN1 and its homolog ATXN1L interact with and stabilize CIC. The AXH domain of ATXN1/ATXN1L and the highly conserved N-terminal region of CIC-S, including amino acid residues 28–48, mediate their interaction (Fig. 1a). ATXN1L plays a more pivotal role in the stabilization of CIC than ATXN1; CIC levels decreased more substantially in response to the loss of ATXN1L than to the loss of ATXN1, leading to substantial derepression of CIC target gene expression. In the absence of ATXN1L, CIC becomes unstable, resulting in proteasomal degradation. ATXN1L also promotes CIC binding to the target gene promoter regions. However, the reason for the relative importance of ATXN1L for CIC stabilization and function is unclear.

Long noncoding RNA (lncRNA)-mediated regulation of CIC expression has been reported. The levels of CIC and lncRNA-AC006129.1, of which genomic locus is close to CIC in chromosome 19, were significantly decreased and increased in samples from schizophrenia patients, respectively. AC006129.1 transgenic mice exhibited social interaction deficits, spatial working memory impairments, and sensorimotor gating disruption accompanied by upregulation of inflammatory response genes, including SOCS3 and CASPI, which are CIC target genes. The overexpression of AC006129.1 downregulated CIC levels in both mouse and human cells, suggesting that this lncRNA-mediated transcriptional repression of CIC expression might be conserved in mammals. Mechanistically, AC006129.1 recruits DNA methyltransferases 1 and 3a (DNMT1 and DNMT3a) and induces DNA methylation of CIC promoter regions.
The AC006129.1-mediated suppression of CIC expression leads to derepression of SOCS3 and CASP1, potentially contributing to the pathogenesis of schizophrenia.62

Concluding remarks
CIC has multiple roles in various developmental processes and in the pathogenesis of various diseases. CIC is believed to function as a tumor suppressor in various types of cancer and is a regulator of embryogenesis, brain and immune cell development, and stem cell maintenance. Our current understanding of CIC functions in mammals is largely limited to processes regulated by the CIC-ETV1/ETV4/ETV5 axis. Many molecular studies of mammalian cells have identified additional target genes of CIC, such as Spry4, Dusp4, Dusp6, Sprea1, Cencl1, Cene1, and Per215,17,27,39,63,64. It will be important to clarify the effects of CIC regulation of various target genes at both the cellular and organismal levels. Furthermore, the mechanism by which CIC regulates target gene expression remains largely unclear and should be a focus of future research. CIC was shown to recruit the histone deacetylase complex to repress the expression of target genes in various biological processes. Finally, CIC is emerging as a key determinant of immune responses. A few studies have recently uncovered the roles of CIC in the development of T cell subsets26,33,34. However, the function of CIC in other types of immune cells, including B cells, dendritic cells, and macrophages, has not been established. Comprehensive studies of CIC functions in various types of immune cells will improve our understanding of the pathogenesis of immune disorders, such as autoimmune diseases and lymphomas, at the molecular level.

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