Gene Section
Review

DDIT4 (DNA-damage-inducible transcript 4)

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Identity

Other names: Dig2, REDD-1, REDD1

HGNC (Hugo): DDIT4

Location: 10q22.1

DNA/RNA

Description

The DDIT4 gene encompasses 2,1 kb, containing 3 exons. Exon 1 includes 142 nucleotides and is non-coding, exon 2 (265 nucleotides) codifies for the first 65 amino acids, and exon 3 (1345 nucleotides) codifies for the remaining 167 amino acids and contains the 3' UTR (NM_019058.2).

Transcription

A single mRNA of 1748 nucleotides is expressed from the plus strand and includes a 699 coding sequence, a 201 5' UTR and a 848 3' UTR (ENST00000307365, Ensembl Genome Browser database). Note minor discrepancy in non-coding region (4 nucleotides) between NCBI and Ensembl annotation.

Protein

Note

REDD1 is a highly conserved protein of 232 amino acids, with a predicted molecular weight of 25 kDa. Apparent molecular weight on SDS-PAGE is 35 kDa. Amino acid sequence analyses do not show any known structural or functional domains. The crystal structure revealed a new fold and a conserved surface patch that is essential for function (Vega-Rubin-de-Celis et al., 2010).

Description

REDD1 is conserved from insects to humans, especially in the C-terminal region (Vega-Rubin-de-Celis et al., 2010).
The N-terminal 84 amino acids of REDD1 are dispensable for function. The REDD1 crystal structure includes residues 89-226 and has a deletion of a few hydrophobic residues (200-204) that are dispensable for function (Vega-Rubin-de-Celis et al., 2010).
The REDD1 protein has two antiparallel α-helices followed by a mixed β-sheet, containing 4 β-strands ordered 2134.
Strands β1-β3 make an unusual structural motif known as a psi-loop, two antiparallel strands separated by a third that makes hydrogen bonds with the two flanking strands.
A conserved surface patch that is essential for REDD1 function has been identified. This patch is formed by two regions: a loop between helix α2 and strand β1 (residues 138-141) and residues 218-225, which encompass the C-terminal portion of the strand β4.
REDD1 is an unstable protein, with an estimated half-life of 5-10 min (Kimball et al., 2008; Katiyar et al., 2009). REDD1 has been shown to be phosphorylated at T23 and T25 and phosphorylation at these sites has been postulated to regulate REDD1 half-life.
These sites are in an N-terminal region that is dispensable for mTORC1 inhibition (Vega-Rubin-de-Celis et al., 2010).
Based on in vitro kinase assays, it was postulated that the kinase implicated in REDD1 phophorylation is Glycogen Sinthase Kinase 3β (GSK3β).
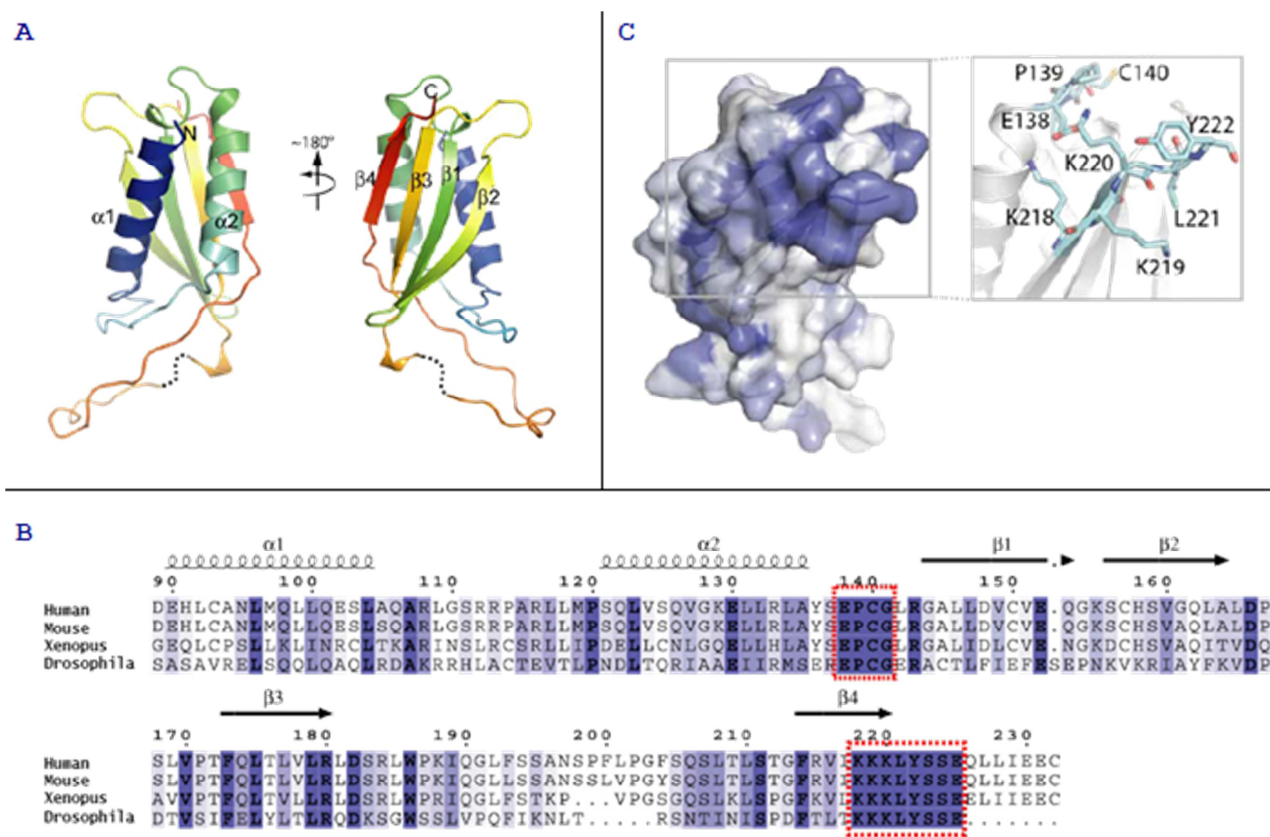
REDD1 crystal structure (PDB ID: 3LQ9). A) Cartoon diagram of REDD1 (89-226Δ200-204) structure colored in rainbow mode from N- to C- terminus. Dotted line represents a disordered region. **B)** REDD1 sequence alignment in different species colored in blue gradient according to conservation. Red boxes indicate the sequences forming the conserved functionally important surface patch. **C)** Conservation mapping of REDD1 surface using the blue gradient color as in (B). Modified with permission from Vega-Rubin-de-Celis et al., Biochemistry, 2010. Copyright (2010) American Chemical Society.

HA-GSK3β isolated from transfected HEK293 cells can phosphorylate GST-REDD1 (Katiyar et al., 2009). However, whether GSK3β phosphorylates endogenous REDD1 is still unknown. How these phosphorylation events are implicated in REDD1 stability is also unclear. Katiyar et al. reported a modest increase in REDD1 half-life upon treatment with LiCl, a GSK3β inhibitor, in HEK293 cells. In addition, REDD1 T23A/T25A mutants transfected in HEK293 cells are more stable than wild-type REDD1. However, [35]S Methionine/Cysteine pulse-chase experiments in HeLa cells suggested that REDD1 wild-type and the T23A/T25A mutants have a similar half-life and LiCl had no effect on the half-life of endogenous REDD1 in these cells (Vega-Rubin-de-Celis and Brugarolas, unpublished results).

REDD1 half-life has been proposed to be regulated by the CUL4A-DDB1-ROC1-βTRCP-E3 ubiquitin ligase complex (Katiyar et al., 2009). In overexpression experiments in HEK293 cells, Flag-REDD1 was found to interact with the complex components Myc-CUL4A, AU1-DDB1 and HA-βTRCP.

In addition, endogenous REDD1 was shown to bind to DDB1 and βTRCP in MCF-7 cells exposed to hypoxia and the proteasome inhibitor MG132 (Katiyar et al., 2009). Furthermore, knock-down of βTRCP by siRNA

in MCF-7 cells increased the REDD1 half-life to 25 minutes (Katiyar et al., 2009). Knock-down of other complex components (CUL4A and DDB1) also increased REDD1 half-life, but to a lesser extent (10-15 minutes) (Katiyar et al., 2009).

Several large-scale proteomic studies showed that REDD1 is ubiquitinated at K129 (Meierhofer et al., 2008; Xu et al., 2010; Danielsen et al., 2011; Kim et al., 2011; Lee et al., 2011; Shi et al., 2011; Wagner et al., 2011). Whether this modification affects REDD1 stability (or function) is unknown and K129 is not conserved across species.

Thioredoxin-Interacting protein (TXNIP) has been shown to bind to REDD1 and TXNIP overexpression in HeLa and H1299 cells increased REDD1 levels (Jin et al., 2011). However, these experiments were performed with ectopically expressed protein and whether the endogenous proteins interact and whether TXNIP regulates REDD1 stability remains to be determined.

A yeast-two hybrid screen of a human leukocyte library reported several putative binding proteins (Gery et al., 2007), and other studies identified other REDD1 interacting proteins including TXNIP (DeYoung et al., 2008; Jin et al., 2011). However, none have been validated with endogenous REDD1 protein.

Expression

REDD1 is developmentally regulated. Redd1 expression has a similar pattern as p63, being expressed at early stages in the apical ectodermal ridge and later on, at ectoderm-derived tissues (Ellisen et al., 2002). Interestingly, p63-/- embryos have lower Redd1 levels suggesting that p63 is an important developmental regulator of REDD1 (Ellisen et al., 2002).

REDD1 mRNA is broadly induced in response to hypoxia (Shoshani et al., 2002; Wolff et al., 2011). Using mice with a gene trap reporter (β-geo) inserted in Redd1 intron 2, Wolff et al. showed that Redd1 is induced after 1h of hypoxia in most of the tissues analyzed, with the exception of cardiac and skeletal muscle. Redd1 was broadly induced in endothelial cells as well as in cells in the crypts of the small bowel, bronchial epithelial cells, cells in zone 3 in the liver, cells lining the collecting ducts of the kidney, red pulp and histiocytes in the spleen and Purkinje cells in the cerebellum (Wolff et al., 2011).

REDD1 is a hypoxia inducible factor (HIF) target (Shoshani et al., 2002). HIF-1 and -2 are heterodimeric transcription factors containing an α-subunit that is regulated by oxygen levels through hydroxylation (Ivan et al., 2001; Jaakkola et al., 2001; Masson et al., 2001; Yu et al., 2001) and a β-subunit (also called aryl hydrocarbon receptor nuclear translocator, ARNT) that is stable (Semenza, 2006).

Hydroxylated HIFα is recognized by an ubiquitin ligase complex containing the von Hippel-Lindau (pVHL) tumor suppressor protein (Cockman et al., 2000; Kamura et al., 2000; Ohh et al., 2000; Tanimoto et al., 2000).

It has been shown in cell lines and mouse models that REDD1 induction is VHL and HIF-dependent (Kucejova et al., 2011). REDD1 is a target of both HIF1α and HIF2α, as assessed by ChIP assays and siRNA experiments in clear cell renal cell carcinoma (ccRCC) cell lines 786-O, A498 and Caki-2 (Kucejova et al., 2011).

MEFs deficient for ataxia telangiectasia mutated (ATM) are unable to induce HIF1α (and REDD1) in response to hypoxia suggesting that, at least in some contexts, ATM may be required for HIFα stabilization (Cam et al., 2010).

Besides hypoxia, REDD1 is also induced in response to a variety of other stress conditions, including ER stress (Wang et al., 2003; Whitney et al., 2009), osmotic stress (Wang et al., 2003) and in response to DNA-damaging agents (Ellisen et al., 2002; Lin et al., 2005a). Other REDD1 inducers include glucocorticoids (Wang et al., 2003; Boldizsar et al., 2006) and all-trans-retinoic acid (ATRA) (Gery et al., 2007).

Apart from HIF1 and 2, other transcription factors have been implicated in REDD1 induction:

- ATF4 (activating transcription factor 4): REDD1 is induced under ER stress conditions in an ATF4-dependent manner (Whitney et al., 2009). Experiments performed in HepG2 cells showed REDD1 induction with the ER stress inducers Thapsigargin and Tunicamycin. This induction was shown to be protein kinase RNA-like ER kinase (PERK) and ATF4-dependent based on studies on PERK or ATF4-deficient MEFs. In addition, ectopically overexpressed ATF4 was sufficient to induce REDD1 expression in HEK293.

- CREBP (CCAAT/enhancer-binding protein): DNA-damaging agent MMS induces REDD1 mRNA in HaCaT cells in a CREBP-dependent manner (Lin et al., 2005a). Luciferase reporter assays identified a MMS-responsive region within -1057/-981 (Lin et al., 2005a) which included a putative CREBP site at -1009/-999, and CREBP was found to bind to this sequence in EMSA.

- Elk1: REDD1 mRNA is induced in HaCaT cells exposed to arsenite, in a Elk1 and CCAAT/enhancer-binding protein (CREBP)-dependent manner (Lin et al., 2005b). Luciferase reporter assays in HaCaT cells mapped the arsenite-responsive region to the -1057/-981 (Lin et al., 2005b), and EMSA assays showed CREBP binding to that region.

- NFATc3 (nuclear factor of activated T-cell): in intestinal cells REDD1 is induced by the NFAT activators PMA and A23187, and siRNA knockdown of NFATc3 but not other family members compromised PMA/A23187-induced REDD1 expression (Zhou et al., 2012). Luciferase-reporter assays showed that NFATc3 was sufficient to activate expression of REDD1 promoter sequences and ChIP assays in HT29 cells showed binding of NFATc3 (-2931/-97) (Zhou et al., 2012).

- p53: MEFs treated with ionizing radiation induced REDD1 in a p53-dependent manner, and overexpression of p53 in SAOS and U2OS cells induced REDD1 (Ellisen et al., 2002). Luciferase reporter assays in U2OS cells identified a p53-responsive element at -600 bp (Ellisen et al., 2002).

- Sp1: REDD1 levels are increased in high cell densities in a Sp-1 dependent manner (Jin et al., 2007). Sp1 siRNA in HeLa cells abolished REDD1 induction by high cell density. Sp1 can also contribute to REDD1 induction in hypoxia or in response to hypoxia mymetics (Jin et al., 2007), and siRNA experiments compromised CoCl2-dependent REDD1 induction. The putative Sp1 binding site was mapped to -476/-446 of the REDD1 promoter by luciferase-reporter assays in HeLa cells (Jin et al., 2007).

The REDD1 promoter region contains putative target sequences for other transcription factors, including NFkB and hepatocyte-nuclear factor 4 (HNF4) (Lin et al., 2005b).

Localisation

REDD1 has been reported to be localized in both nuclear and cytosolic compartments in overexpression experiments (Ellisen et al., 2002; Lin et al., 2005b). Biochemical fractionation studies of the endogenous

protein did not show REDD1 in the nucleus, but indicated that REDD1 is both in a cytosolic and a membrane compartment (DeYoung et al., 2008). In Redd1-/- MEFs transduced with a retroviral vector encoding for REDD1, REDD1 localized to the mitochondria (Horak et al., 2010). Further studies are required with the endogenous protein. However, preliminary experiments (both in normoxia and hypoxia conditions) suggest that REDD1 is in the cytosol and that it is peripherally associated with a membrane compartment (Vega-Rubin-de-Celis et al., unpublished results).

Function

REDD1 is induced in hypoxia and is both necessary and sufficient for hypoxia-induced mammalian target of rapamycin complex 1 (mTORC1) inhibition (Brugarolas et al., 2004). MEFs deficient for Redd1 (Brugarolas et al., 2004; DeYoung et al., 2008; Wolff et al., 2011) fail to inhibit mTORC1 in response to hypoxia, and depletion experiments with siRNAs or shRNA in HeLa, HEK293 and U937 cells compromised hypoxia-induced mTORC1 inhibition (Corradetti et al., 2005; Gery et al., 2007; Vega-Rubin-de-Celis et al., 2010). Overexpression of REDD1 in multiple cell types including U2OS (Brugarolas et al., 2004; Sofer et al., 2005; DeYoung et al., 2008; Vega-Rubin-de-Celis et al., 2010), HeLa (Vega-Rubin-de-Celis et al., 2010), MEFs (Sofer et al., 2005), and HEK293 (Corradetti et al., 2005) cells is sufficient for mTORC1 inhibition.

REDD1 has a paralogue, REDD2 (DDIT4-like (DDIT4-L) or RTP801-like (RTP801-L)). REDD1 and REDD2 appear to be have originated from a gene duplication event that occurred independently in humans and insects (Vega-Rubin-de-Celis et al., 2010). However, unlike Redd1, Redd2 is not induced by hypoxia, at least in MEFs (Wolff et al., 2011). Nevertheless, like REDD1, REDD2 overexpression is sufficient to inhibit mTORC1 (Brugarolas et al., 2004). The Drosophila orthologues, scylla and charybdis, were identified in a screen to isolate inhibitors of an increased cell size phenotype generated by simultaneously expressing PDK1 and Akt (Reiling and Hafen, 2004). Both genes contain consensus hypoxia-response elements (HRE) sequences (Reiling and Hafen, 2004). Scylla expression is also induced in response to hypoxia in the larval fat body and the gut. Charybdis mRNA was not induced in the fat body and only slightly in the midgut (Reiling and Hafen, 2004). In addition, charybdis is not induced through overexpression of constitutively active Drosophila HIFα (sima) or Hifβ (tgo) (Reiling and Hafen, 2004). Even though REDD1 induction broadly inhibits mTORC1, under some conditions (and for reasons that are not understood), this is not the case in ccRCC. VHL is inactivated in a majority of ccRCC cases, leading to stabilization of HIF1/HIF2 and increased REDD1

levels. However, REDD1 does not appear to inhibit mTORC1, and mTORC1 is frequently activated in ccRCC (Kucejova et al., 2011).

Hypoxia-induced mTORC1 inhibition is dependent on the tuberous sclerosis complex 1 and 2 proteins, which form a complex (TSC1/TSC2). This has been shown in a variety of systems. Tsc2-/- MEFs fail to inhibit mTORC1 when exposed to hypoxia or to ectopic Redd1, but they regain their ability to inhibit the pathway after Tsc2 reconstitution (Brugarolas et al., 2004; Corradetti et al., 2005; Sofer et al., 2005). Depletion of TSC2 with siRNA in U2OS, HeLa, HEK293 and MCF10A cells also compromises mTORC1 inhibition by hypoxia or REDD1 overexpression (Brugarolas et al., 2004; Connolly et al., 2006; Vega-Rubin-de-Celis et al., 2010).

However, hypoxia-induced mTORC1 inhibition can also occur independently of mTORC1. In hepatocytes, mTORC1 inhibition by hypoxia is REDD1-independent. In this cell type, hypoxia signals are transduced in a manner that is also independent of Tsc1/Tsc2 and Hif (Wolff et al., 2011).

It was suggested that REDD1 acts by sequestering 14-3-3 proteins from TSC2 thereby activating TSC2 and inhibiting mTORC1 (DeYoung et al., 2008). However, how REDD1 would selectively sequester TSC2-bound 14-3-3 versus the whole 14-3-3 pool in the cell, which is quite large, is not clear. Furthermore, the putative 14-3-3 binding site in REDD1 does not conform to any of 14-3-3 binding sites known (Vega-Rubin-de-Celis et al., 2010), and endogenous REDD1 does not seemingly bind to 14-3-3 proteins. Moreover, the postulated 14-3-3 binding motif in REDD1 ([133]RLAYSEP[139]) is not conserved, and mutations of R133 and S137 that might have expected to be critical for 14-3-3 binding do not abrogate REDD1 function (Vega-Rubin-de-Celis et al., 2010).

REDD1 is developmentally regulated in both flies and in mice, but Redd1 is dispensable for development in mice (Brafman et al., 2004; Yoshida et al., 2010; Molitoris et al., 2011; Wolff et al., 2011). In addition, loss of both scylla and charybdis does not cause lethality in flies. However, their loss severely compromised larval survival in hypoxia conditions (Reiling and Hafen, 2004). Interestingly, disruption of Redd1 in mice does not result in a compensatory induction by the paralogue Redd2, which has been shown to also inhibit mTORC1 in overexpression experiments in HeLa cells (Brugarolas et al., 2004).

Mutations

Note

A frameshift inactivating mutation (c.550delC) was found in ccRCC (Kucejova et al., 2011).

However, no other REDD1 mutations where identified in sequencing analyses of 77 tumors.

Somatic

A somatically acquired mutation was identified in a pancreatic tumor (c.571G>T; p.G191W) (Sanger Institute, COSMIC database). While the residue is not conserved, according to PolyPhen-2, the mutation is probably damaging, but whether it affects function is unclear.

A mutation in prostate cancer (c.253A>C; p.S85R) has been described (Sanger Institute, COSMIC database).

It is unknown whether the mutation was somatically acquired and according to PolyPhen-2 it is probably damaging.

An additional somatically acquired mutation was found in prostate carcinoma (c.253A>C); however, it is a synonymous substitution (p.L96L) (Sanger Institute, COSMIC database).

Two mutations have been detected in lung squamous cell carcinoma (G75R and A37V) (Hammerman et al., 2012, cBIO Cancer Genomics). They are both somatically acquired (Sanger Institute, COSMIC database), and according to PolyPhen-2 they are predicted to be benign.

Two mutations have been identified in uterine corpus endometrioid carcinoma (H91R and R143W) (cBIO Cancer Genomics).

They are somatically acquired, (Sanger Institute, COSMIC database) and according to PolyPhen-2 they are predicted to be benign (H91R) or probably damaging (R143W).

A somatically acquired mutation was identified in two samples of lung carcinoma (c.4C>T; p.P2S) (Sanger Institute, COSMIC database). Pro2 residue is in a dispensable region in REDD1; however, according to Polyphen2 is probably damaging.

A synonymous somatically acquired substitution mutation was also described in lung carcinoma (c.561C>G; p.P187P) (Sanger Institute, COSMIC database).

A somatically acquired mutation was identified in cervix carcinoma (c.79G>C; p.D27H) (Sanger Institute, COSMIC database).

It is in a dispensable region in REDD1 and predicted to be benign based on Polyphen2.

In urinary tract carcinoma samples a somatically acquired mutation was found (c.671C>T; p.S224L) (Sanger Institute, COSMIC database).

It is predicted to be probably damaging by Polyphen2.

Implicated in

Cancer

Note

DDIT4 has been shown to be mutated in a handful of cancers at low frequency. However, mutations may not be detrimental and while it would be fitting for a negative mTORC1 regulator to act as a tumor suppressor, whether this is the case remains to be determined and no tumor predisposition has been reported in Ddit4-deficient mice.

Interestingly, REDD1 is over expressed in most of the ccRCC tumors, due to the loss of pVHL and HIF1/HIF2 stabilization. Paradoxically this increase does not lead to mTORC1 inhibition, and mTORC1 is usually activated in ccRCC (Kucejova et al., 2011).

Viral infection

Note

REDD1 has been recently implicated as a host defense factor in response to viral infections. In Redd1-/- MEFs, there is increased viral protein translation after viral infection in a mTORC1 dependent manner (Mata et al., 2011). Treatment with Rapamycin downregulated viral proteins in both Redd1+/+ and Redd1-/- MEFs, suggesting that the mTORC1 is implicated in viral protein synthesis. Naphthalimides (which inhibit NS1, an influenza A virus virulence factor) induce REDD1 and inhibit mTORC1 thereby reducing viral protein production. REDD1 may be essential for their antiviral effect, as the antiviral effect was abolished in Redd1-/- cells. Similarly, in Tsc2-/- cells naphthalimides failed to downregulate viral protein expression.

Parkinson disease

Note

Redd1 was found to be increased in cellular and animal models of Parkinson disease (Malagelada et al., 2006; Malagelada et al., 2008). It has been shown to increase neuronal cell death through a mechanism involving mTORC1 and Akt. In PC12 cells treatment with 6OHDA induces Redd1 and increases cell death; this phenotype is rescued by knock-down of Redd1. Furthermore, Redd1 overexpression is sufficient to induce cell death.

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