Gene Section
Mini Review

CRTC2 (CREB regulated transcription coactivator 2)
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Identity
Other names: TORC2, RP11-422P24.6
HGNC (Hugo): CRTC2
Location: 1q21.3

DNA/RNA
Description
10,893 bases; on minus strand.
Includes 14 exons.

Transcription
Transcript measures 2598 bp with a 2082 bp coding sequence.

Protein
Description
693 amino acids; 73,302 Da.

Expression
Particularly abundant in B and T lymphocytes. Higher levels were also seen in muscle, lung, spleen, ovary and breast. Lower expressions found in brain, colon, heart, kidney, prostate, small intestine and stomach, with significantly lowest expression in liver and pancreas.

Localisation
Phosphorylation of CRTC2 triggers the phosphorylation-dependent binding to 14-3-3 proteins, and hence sequestration of CRTC2 in the cytosol thereby preventing its nuclear translocation and the activation of CREB. Proteins known to phosphorylate CRTC2 at Ser171 include AMP-activated protein kinase (AMPK) and the salt-inducible kinases (SIKs). Dephosphorylated CRTC2 readily translocates to the nucleus. CRTC2 contains a nuclear localisation sequence (NLS) at amino acids 56-144 as well as two nuclear export sequences (NES1 and NES2) within the region of amino acids 145-320.

Function
Transcriptional coactivator for CREB (cAMP-responsive element binding protein). The highly conserved N-terminal coiled-coil domain of the CRTC2 interacts with the bZip domain of CREB which activates both consensus and variant cAMP response element (CRE) sites, leading to activation of CREB target gene expression. CRTC2 responds to stimulation by cAMP, calcium, fasting hormones, G protein-coupled receptors, and AMPK/SIKs.

Implicated in
Peutz-Jeghers syndrome
Note
Peutz-Jeghers syndrome (PJS) is an autosomal-dominant genetic disorder that is characterised by an increased risk of developing malignant tumours. Most of the identified mutations in the LKB1 gene are localised to the catalytic kinase domain so that it is thought that PJS results from loss of LKB1 kinase activity. The silencing of LKB1, leads to the decreased activity of AMPK and SIK and leads to the increased nuclear translocation and activity of CRTC2.

Disease
Gastrointestinal polyps and cancers including esophagus, stomach, small intestine, colon, pancreas, lung, testes, breast, uterus, ovary and cervix.

Oestrogen-receptor (ER) positive breast cancer
Note
The increased prevalence of oestrogen-dependent, postmenopausal breast cancers is correlated with
elevated local levels of oestrogens as a result of an increase in cytochrome P450 aromatase expression within the adipose stromal (hAS) cells surrounding the breast tumour - aromatase is the enzyme responsible for the conversion of androgens to oestrogens. This is governed by promoter switching from the distal promoter I.4 to the proximal promoter PII on the CYP19A1 gene, that encodes aromatase, in response to factors derived from the tumour such as prostaglandin E2 (PGE2). Interestingly, the LKB1/AMPK pathway has been shown to inhibit aromatase expression via the cytoplasmic sequestration of CRTC2. However, PGE2 inhibits LKB1/AMPK signaling, leading to the nuclear translocation of CRTC2 and its enhanced binding and activation of aromatase promoter PII in hAS cells. Furthermore, the adipokine leptin, produced at higher levels in obesity, has been shown to cause an increase in CRTC2 nuclear translocation and consequently, in aromatase expression.

References


Brown KA, Simpson ER. Obesity and breast cancer: progress to understanding the relationship. Cancer Res. 2010 Jan 1;70(1):4-7

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