Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Review

ADRB2 (adrenoceptor beta 2, surface)

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Abstract

Review on ADRB2, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: ADRB2R, ADRBR, B2AR, BAR, BETA2AR

HGNC (Hugo): ADRB2

Location: 5q32

DNA/RNA

Description

ADBR2 gene spans about 2,04 kb and consists of one exon.

Transcription

ADBR2 no has introns in either their coding or untranslated sequences. The primary transcripts are processed at their 5' and 3' ends like other premessenger RNAs, but no splicing is needed.

Pseudogene

No pseudogenes have been reported.

Protein

Description

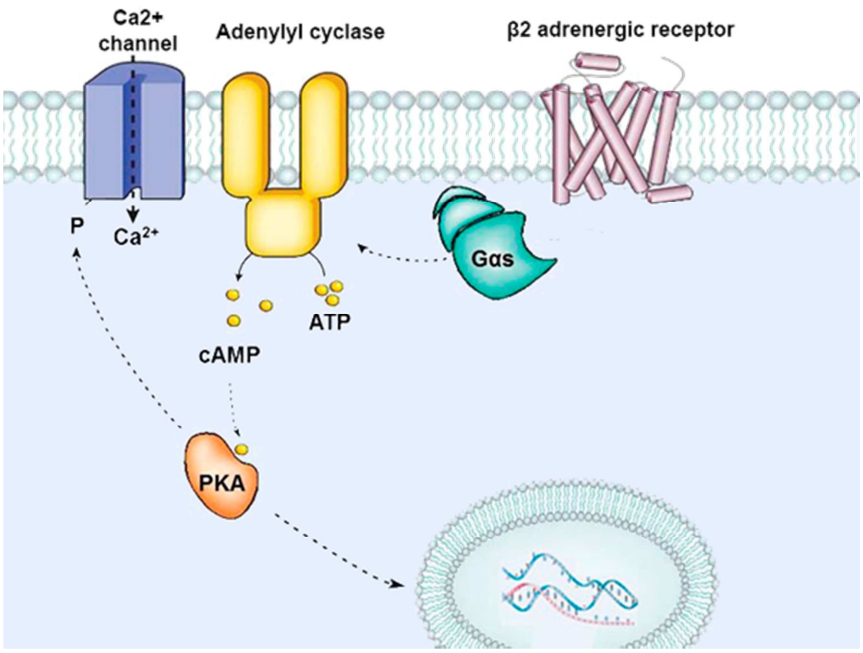
β2 adrenergic receptor is a member of the superfamily of G-protein coupled receptors (GPCRs) (McGraw and Liggett, 2005; Johnson, 2006). The receptor is comprised of 413 amino acid residues of approximately 46500 daltons (Johnson, 2006). β2 adrenergic receptor is N-glycosylated at amino acids 6, 15, and 187; these are important for roper insertion of the receptor into the membrane as well as for agonist trafficking (McGraw and Liggett, 2005; Johnson, 2006).

Expression

β2 adrenergic receptor is widely distributed, this protein is expressed by airway smooth muscle (30-40000 per cell), epithelial and endothelial cells of the lung, smooth muscle of blood vessels, skeletal muscle, mast cells, lymphocytes, oral and skin keratinocytes and also by diverse cancer cells (Kohm and Sanders, 2001; Lutgendorf et al., 2003; Johnson, 2006; Sood et al., 2006; Thaker et al., 2006; Yang et al., 2006; Sastry et al., 2007; Yu et al., 2007; Liu et al., 2008a; Liu et al., 2008b; Shang et al., 2009; Sivamani et al., 2009; Yang et al., 2009; Bernabé et al., 2011; Bravo-Calderón et al., 2011-2012; Steenhuis et al., 2011; Zhang et al., 2011; Loenneke et al., 2012).

Localisation

β2 adrenergic receptor is a transmembrane protein. Like all GPCRs, the β2 adrenergic receptor has seven transmembrane a domains that form a pocket containing binding sites for agonists and competitive antagonists (McGraw and Liggett, 2005; Johnson, 2006). There are 3 extracellular loops, with one being the amino terminus, and 3 intracellular loops, with a carboxy terminus (McGraw and Liggett, 2005; Johnson, 2006).



Activation of protein kinase A (PKA) by signal transduction of β2 adrenergic receptor (adapted of Rosenbaum et al., 2009).

Function

Agonist binding of β2 adrenergic receptor results in activation of Gs protein. The Gs protein a subunit stimulates adenylyl cyclase to generate cyclic 3'-5'-adenosine monophosphate (cAMP), which in sequence activates the cAMP-dependent protein kinase A (PKA) and the agonist-occupied receptor is phosphorylated.

After phosphorylation, the receptor switches its coupling specificity to Gi. GTP-bound Giα dissociates from the heterodimeric Gβγ, and free Gβγ subunits mediate activation of the MAP kinase signaling pathway in the same way as Gi-coupled receptors. Increase of intracellular cAMP levels leads diverse cell functions as cell proliferation, differentiation, angiogenesis and migration (Daaka et al., 1997).

Implicated in

Ovarian carcinoma

Note

Reverse transcriptase-PCR studies indicated constitutive expression of β2 adrenergic receptor on ovarian carcinoma cell lines (Lutgendorf et al., 2003). Lutgendorf et al. (Lutgendorf et al., 2003) investigated the effects of norepinephrine and isoproterenol (a nonspecific-adrenergic agonist) on the production of vascular endothelial growth factor (VEGF) by ovarian cancer cell lines; and found that both, norepinephrine and isoproterenol, significantly enhanced VEGF production. These effects were blocked by thenon-specific β antagonist propranolol, supporting a role foradrenergic receptors in these experimental effects.

Norepinephrine was later found to increase the in vitro invasive potential of ovarian cancer cells, an effect that was blocked by propranolol (Sood et al., 2006). Norepinephrine also increased tumor cell expression of matrix metalloproteinase-2 (MMP-2) and MMP-9, and pharmacologic blockade of MMPs abrogated the effects of norepinephrine on tumor cell invasive potential (Sood et al., 2006).

In the same way, Thaker et al. (Thaker et al., 2006) correlated chronic behavioral stress with higher levels of tissue catecholamines and more invasive growth of ovarian carcinoma cells in an orthotopic mouse model. These effects were mediated through β2 adrenergic receptor activation of PKA signaling pathway (Thaker et al., 2006). Tumors in stressed animals showed increased vascularization and enhanced expression of VEGF, MMP2 and MMP9; these effects could be abrogated by propranolol (Thaker et al., 2006).

Prostate cancer

Note

β2 adrenergic receptor signaling was related to prostate cancer cell progression (Sastry et al., 2007; Zhang et al., 2011). β2 adrenergic receptor activation of PKA signaling pathway has been associated with reduction of sensitivity of prostate cancer cells to apoptosis (Sastry et al., 2007) and promotion of cell proliferation and cell migration (Zhang at al., 2011).

Contrastingly, other investigation demonstrated that the genetic silencing of β2 adrenergic receptor increases cell migration and invasion of normal

prostate cells and that the weak expression of this protein is associated with metastases and with worst survival rates in prostate cancer patients (Yu et al., 2007).

Esophageal squamous cell carcinoma

Note

Liu et al. (Liu et al., 2008b) demonstrated that stimulation of β2 adrenergic receptor with epinephrine significantly increase the esophageal cancer cell proliferation accompanied by elevation of the expression of VEGF, VEGF receptor VEGFR-1 and VEGFR-2. In addition, it has been shown that the epidermal growth factor mediates the mitogenic signals in esophageal cancer cells through transactivation of β2 adrenergic receptor (Liu et al., 2008a).

Oral squamous cell carcinoma (OSCC)

Note

Genetic and protein expression of β2 adrenergic receptor was demonstrated in OSCC by using RT-PCR assay, Western blot and immunohistochemistry (Shang et al., 2009; Bernabé et al., 2011; Bravo-Calderón et al., 2011-2012). Investigations performed in different oral cancer cell lines demonstrated that β2 adrenergic receptor signaling by norepinephrine increases cell proliferation and invasion, and upregulates interleukin-6 (IL-6) gene expression and protein release (Shang et al., 2009; Bernabé et al., 2011). Furthermore, Shang et al. (Shang et al., 2009) reported that malignant cell positive immunoexpression of β2-AR was significantly correlated with age, tumor size, clinical stage and cervical lymph node metastasis in OSCC patients, and that β2-AR may play an important role in the formation and metastasis of oral cancer. However, a retrospective clinical study of a large number of patients showed that patients with OSCC who exhibited strong β2-AR immunohistochemical expression by malignant epithelial cells demonstrated higher survival rates compared to patients with weak/negative β2-AR expression (Bravo-Calderón et al., 2011-2012). Therefore, further clinical and laboratory studies are warranted to elucidate the role of β2 adrenergic receptor activation in oral squamous cell carcinoma.

Various cancers

Note

β2 adrenergic receptor was also immunohistochemically identified in nasopharyngeal carcinoma (Yang et al., 2006) and in melanoma (Yang et al., 2009). Norepinephrine treatment increased MMP-2, MMP-9, and VEGF levels in culture supernatants of nasopharyngeal carcinoma cells lines (Yang et al., 2006); as well upregulated the production of VEGF, interleukin (IL)-8, and IL-6 in human melanoma tumor cell lines (Yang et al., 2009).

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