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Gene Section
Review

ATP5B (ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide)

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Abstract

Review on ATP5B, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: ATPMB, ATPSB, HEL-S-271

HGNC (Hugo): ATP5B

Location: 12q13.3

DNA/RNA

Description

The human ATP5B gene is located on the minus strand and spans 7894 bps of genomic region (56638175 - 56646068). ATP5B gene sequence shows partial homology with chromosomes 2 and 17. There are 13 Alu repeat sequences. Among these sequences, 4 were found to be inside the intron and the rest were towards the upstream side.

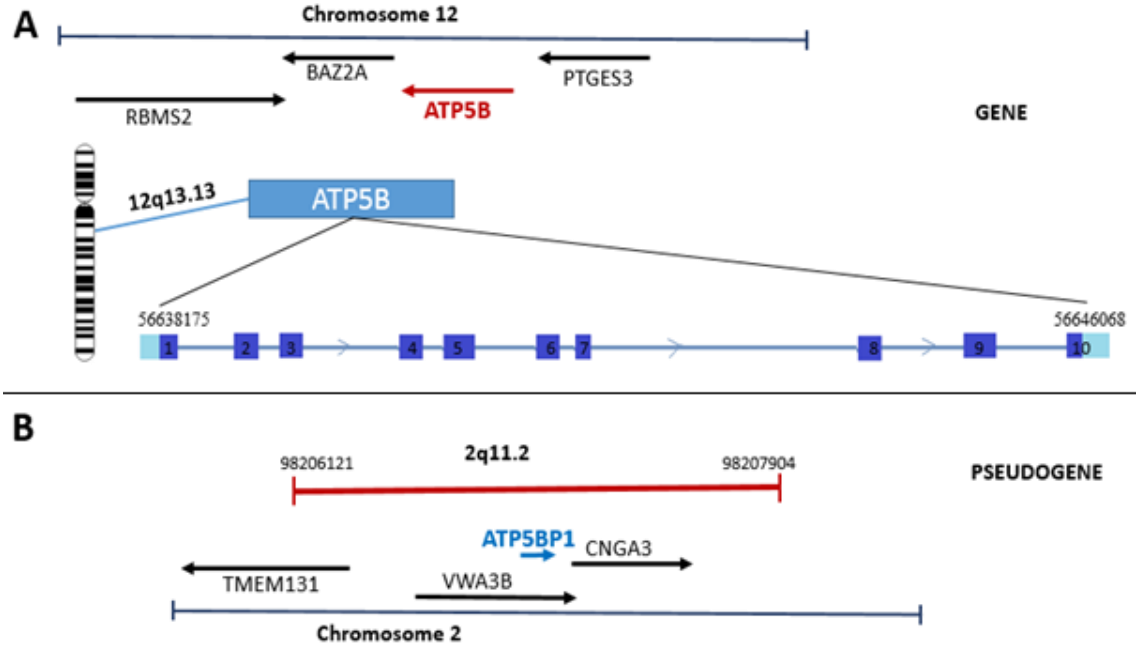

Figure 1. A. Location of ATP5B gene and the representation of its transcript. ATP5B gene is localized on 12q13.13 on minus strand and contains exonic regions. **B.** Location of ATP5BP1 (ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypepide pseudogene 1) and pseudogene.

Figure 2. ATP5B protein sequence data showing beta-barrel domain (brown colored), nucleotide binding domain (blue colored), C terminal domain (green colored), Walker A motif (light pink), Walker B motif (orange colored), polypeptide binding site (black), ATP binding site (chemical binding) (red colored), inhibitor binding site (dark pink).

ATP5B gene consists of four "CCAAT" sequences upstream and these sequences are much closer to the transcriptional initiation site (Neckelmann et al., 1989).

This gene encodes a single transcript as presented in NCBI database. It has 10 exons and mRNA size 1857 bp. It has 529 amino acids (aa) and its size is about 56 kDa (figure 1A).

Transcription

ATP5B gene transcript is assigned in the reference database as well as ensemble data base including 11 splice variants which are described as ENST00000262030, ENST00000552959, ENST00000551020, ENST00000553007, ENST00000551570, ENST00000550162, ENST00000547250, ENST00000547808, ENST00000548647, ENST00000551182, ENST00000548474. The level of mRNA transcript reveals marked differences between tissues. It is mostly expressed in the heart while it is less expressed in the skeletal muscles. It is also less expressed in liver and kidney. These findings suggest that tissue-specific mRNA levels of ATP5B can occur with transcriptional control (Neckelmann et al., 1989). The exact function of ATP5B is not known and the level of ATP5B gene expression has been shown to fall in different human tumors as compared to normal tissues (Willers et al., 2010). ATP5B transcripts were found to be highly expressed in colorectal cancer patients (Geyik et al., 2014).

Pseudogene

A pseudogene named ATP5BP1 has been found on chromosome number 2 with contig number NC_000002.12 (reference GRCh38 Primary Assembly) for ATP5B gene. This pseudogene is encoded in the intronic region of the VWA3B gene. It is localized on 2q11.2 and is also known by other terms like ATP5BL1; ATPMBL1; ATPSBL. It is 1783 nt in length (figure 1B).

Protein

Description

ATP synthase beta subunit which is ATP5B protein and is also known as mitochondrial precursor is encoded by ATP5B gene. During oxidative phosphorylation, it maintains the electrochemical tendency of the protons in the membrane as well as it possess 5 sub units of ATP synthase enzyme like alpha (α), beta (β), gamma (γ), delta (Δ) and epsilon (ε) which acts as a catalyst in ATP synthesis. ATP5B constitutes the beta-subunit of ATP synthase enzyme and this enzyme is formed of 529 amino acid residues. Figure 2 shows that the molecular weight of this protein is 56559.90 g/mol and isoelectric

point is 5.0668. The amino acid sequence of this protein and domain are also shown.
ATP5B protein is composed of three domains: ATP synthase alpha/beta family, beta-barrel domain (63-129 aa), F1 ATP synthase beta subunit nucleotide binding domain (131-420 aa), ATP synthase alpha/beta chain C-terminal domain (418-525 aa). It consists of a large family of proteins consisting of ATP-binding cassette transporter nucleotide-binding domains; ABC transporters, ions, sugar and different components transporting peptides and organic molecules. This nucleotide binding domain resembles to all other members of this family protein. It consists of ABC transporter, the Q-loop, and H-loop/switch region and in addition consists of a subset of nucleotide hydralazine motifs such as Walker A motif/P-loop and Walker B motifs that are mainly found in many hydrolysis proteins and several ATP and GTP-binding proteins.

Expression

In oxidative phosphorylation, the cellular relative expression level of ATP5B protein was compared between normal and tumor tissues. It has been reported that there was less expression in tumor tissues as compared to normal (Cuezva et al., 2004). ATP5B gets down regulated in some cancers and helps to increase the expression of some glycolytic pathway markers. The cell death response with chemical agents shows correlation with oxidative phosphorylation as well as ATP5B expression (Cuezva et al., 2009; Lin et al., 2008; Shin et al., 2005). ATP5B expression was found to be significantly lower in esophageal and breast cancer cells as compared to normal tissues (Acebo et al., 2009). ATP5B protein expression in the cancer tissue was found to be down-regulated as compared to normal tissues (Cuezva et al., 2002; López-Ríos et al., 2007; Willers et al., 2010). The mitochondrial localization and translation of β-F1-ATPase mRNA (termed β-mRNA) are known to be primary sites for regulating the spatial and temporal expression of the protein as it is indicated by the expression of β-F1-ATPase in the liver, in brown adipose tissue and during cell cycle progression.

Localisation

The ATP5B protein is localized to the mitochondrion inner membrane.

Function

As many other proteins, ATP5B has ATP and protein binding functions. The majority of cellular energy is synthesized in the form of ATP by ATP synthase. The force for ATP synthesis eventually comes from Na+ gradient which further activates an electrochemical proton rotation which takes place around F0 motor particles in the membrane.
The effective rotation does not only require DeltamuH(+), membrane containing the potentials (Deltapsi) and proton concentration gradient (DeltapH) but also requires high proton concentration from the P sources (Von Ballmoos et al., 2009).
The enzyme catalyzed oxidation of metabolic substances like glucose, fatty acids and amino acids are transferred to electron carriers.
These electrons are then transferred to the electron transport system (ETS) located in the mitochondrial membrane. ATP synthase enzyme gets activated with the resulting proton gradient.
ATP synthesis takes place by F0-F1 ATP synthase enzyme complex as a result of power produced by protons in the matrix.
ATP5B protein also plays an important role in the oxidative phosphorylation during the formation of beta subunit of F1 unit of ATP synthase enzyme.
In an study conducted with human immunodeficiency virus (HIV)-1, replication was found to be inhibited in HeLa P4 / R5 cells after the siRNA mediated knockdown of ATP5B (Zhou et al., 2008). ATP5B was shown to be upregulated by Tat protein of HIV-1 virus (López-Huertas et al., 2013). ATP5B protein was also shown to be physically interacted with Vpr, a HIV-1 virus protein in HEK293 cells (Barrero et al., 2013).
Metabolic changes are common characteristic features of cancer tissues.
The downregulation of oxidative phosphorylation is a distinguishing feature of many cancer types.
The decrease in expression of subunit of F1 unit of ATP synthase enzyme has been associated with many malignant cancers (Xiao et al., 2013).
Angiostatin which is an angiogenesis inhibitor binds to ATP synthase found on endothelial cell surface and inhibits it.
It also regulates cellular pH in cell acidosis and impairs endothelial cell formation.
The agonist of ATP synthase MAb3D5AB1, recognizes catalytic β-subunit of ATP synthase and inhibits the activity of F1 domain (Chi et al., 2007). Mab3d5ab1 shows angiostatin-like properties and can be useful in the chemotherapy (Chi et al., 2007).

Homology

ATP5B gene sequence shows homology to chromosomes 2 of 17 (Neckelmann et al., 1989). It also shows homology to other organisms in following manner.
It shows homology to P. troglodytes 99%, M.mullata 98%, C. lupus 92%, M. musculus 89%, R. norvegicus 89%, G. gallus 78%, D. melanogaster 74%, C. elegans, 70%, S. cerevisiae 69% (data from NCBI BLAST).

Mutations

There has been no mutation identified in ATP5B till now. However, many variations have been identified

on these genes: approximately 190 single nucleotide variant, 35 missense variant, 20 synonyms variant, 110 intron variant, 11 deletion, 8 insertion, 1 indel, 1 splice donor variant, 3 5'UTR variant, 6 3' UTR variant.

Implicated in

Colorectal cancer

Prognosis

Many studies show low expression of mitochondrial ATP synthase in many cancers including lung cancer, breast cancer and colorectal cancer (Willers et al., 2010).

In addition, shorter life span of colorectal cancer patients has been associated with the low expression of ATP5B gene.

In a study on colorectal cancer patients, ATP5B expression was found to be increased in tumor tissues as compared to normal ones and a significant increase in ATP5B gene expression was found in patients under 45 years of age (Geyik et al., 2014).

Breast cancer

Prognosis

Breast cancer is a common malignancy in women worldwide.

ATP5B was found to be upregulated in breast cancer tissues in a significant manner.

This protein can even play an important role as a target protein in the treatment of cancers. Using ATP synthase inhibitor aurovertin B, in breast cancer cells MCF-7, the effect of ATP5B protein in tumor progression was found to be reduced (Huang et al., 2008).

Lung cancer

Prognosis

Using proteomic technologies, ATP5B has been found to be associated with McAb4E7 antigen. In an immunohistochemical study, an abnormal expression has been shown in non-small cell lung cancer (NSCLC) with McAb4E7 antigen on the cell membrane of tumors but such expression has not been shown in small cell lung cancer (SCLC). Through this particular study, the abnormal expression of ATP5B protein on cell surface can be presented as a potential tumor associated antigen in immunodiagnostic and immunotherapy for NSCLC. ATP5B may be a potential marker and a therapeutic target for immunotherapy in NSCLC on cell surface (Lu et al., 2009).

Hepatocellular cancer

Prognosis

β-F1-ATPase is known to be a high-density lipoprotein (HDL) receptor for apolipoprotein A-I and is localized on the plasma membrane of rat and human hepatocytes and HepG2 cells (Martinez et al., 2003). The expression of ATP5B is controlled during post-transcriptional level of cell cycle and oncogenesis. MiR-127-5p 3'UTR of β-F1-ATPase which shows much expression in fetal liver targets mRNA (β-mRNA). ATP5B expression is reduced in many types of cancer, but miR-127-5p does not show expression in some cancers. miR-127-5p has an important role in regulating the activity of mitochondrial bioenergetics in cancers (Izquierdo and Cuezva, 1997). ATP5B expression in the liver has been shown to be controlled at the post-transcriptional level, and this control was found to be induced by miR-127-5p. miR-127-5p inhibits β-F1-ATPase mRNA translation in humans (Willers et al., 2012).

Acute myeloid leukemia

Prognosis

ATP5B gene expression and ATP synthase activity was found to be downregulated in patients with acute myeloid leukemia (AML). The decline in the activity of the ATP synthase and the downregulation of ATP5B shows a positive correlation to Adriamycin resistance in primary leukemia cells (Li et al., 2009). ATP5B has been shown to play an important role in multi-drug resistance mechanism in relapsed or refractory showing AML patients (Xiao et al., 2013). The upregulation of ATP5B was found to inhibit growth of adriamycin induced leukemia cells and was also found to decrease resistance for adriamycin triggered apoptosis (Xiao et al., 2013).

Other disease

ATP5B gene has been also found to be associated with Alzheimer, Parkinson and Huntington disease. ATP5B and MDH1 were found to be involved in the energy metabolism, whose overexpression in null cell adenomas pave a new way of exploring the oncogenesis of these tumors (Hu et al., 2007).

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