Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Mini Review

PIK3CA (phosphoinositide-3-kinase, catalytic, alpha polypeptide)

Montserrat Sanchez-Cespedes

Programa d'Epigenetica i Biologia del Cancer-PEBC, Institut d'Investigacions Biomediques Bellvitge (IDIBELL), Hospital Durant i Reynals, Avinguda Gran Via de l'Hospitalet, 199-203 08907-L'Hospitalet de Llobregat-Barcelona, Spain (MSC)

Published in Atlas Database: April 2009

Online updated version: http://AtlasGeneticsOncology.org/Genes/PIK3CAID415ch3q26.html
DOI: 10.4267/2042/44713

Identity

Other names: EC 2.7.1.153; MGC142161; MGC14216
PI3K; p110-alpha

HGNC (Hugo): PIK3CA

Location: 3q26.32

Local order: centromere-KCNMB2-ZMAT3-BC032034-PIK3CA-KCNMB3-ZNF639-MFN1-GNB4- telomere

DNA/RNA

Relative size of the 21 exons of PIK3CA. The entire exon 1 is UTR (untranslated region). Exon numeration corresponds to the prevalent transcript (NM-006218).

Description

The PIK3CA gene spans a total genomic size of 86,190 bases and is composed of 21 exons, 20 of them coding exons of varying lengths. Putative pseudogenes of PIK3CA have been described on chromosomes 16 (gi 28913054) and 22q11.2 (gi 5931525), the later one in the Cat Eye Syndrome region. These regions are highly homolog to the sequences of exons 9 and 11-13 of the PIK3CA gene.

Transcription

The human PIK3CA transcript has an open reading frame of 3,207-bp, predicting a protein of 1,068 amino acid residues.

Protein

Description

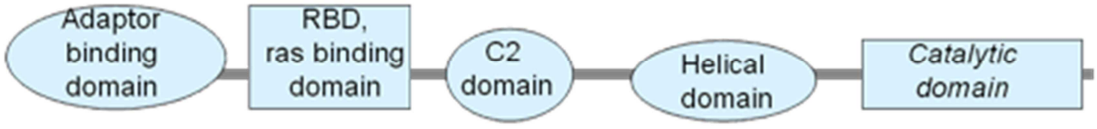
The PIK3CA gene encodes the p110alpha protein which is a catalytic subunit of the class I PI 3-kinases (PI3K). Class I PI3K are heterodimeric molecules composed of a catalytic subunit, a p110, and a regulatory subunit. There are three possible calatytic subunits p110alpha, beta or delta.

Expression

Widely expressed.

Localisation

The p110alpha localizes in the cytoplasm.



p110alpha conserved domains. Through its adaptor binding domain p110alpha interacts with the regulatory subunit. C2 domain, protein-kinase-C-homology-2 domain.

Function

Class I PI 3-kinases (PI3K) are linked to many cellular functions, including cell growth, prolifera-tion, differentiation, motility, survival and intra-cellular trafficking. PI3K convert PI(4,5)P2 to PI(3,4,5)P3 on the inner leaflet of the plasma membrane. The PI(3,4,)P3 provokes the recruitment to cellular membranes of a variety of signalling proteins, containing PX domain, pleckstrin homo-logy domains (PH domains), FYVE domains and other phosphoinositide-binding domains. One of these is the protein kinase B (PKB/AKT) a very well known protein that is activated as a result of its translocation to the cell membrane where it is then phosphorylated and activated by another kinase, called phosphoinositide dependent kinase 1 (PDK1). The phosphorylation of AKT leads to the activation of the TSC/mTOR pathway. PTEN, a tumor suppressor inactivated in many cancers counteracts the action of PI3K by dephosphoryla-ting the phosphoinositide-3,4,5-trisphosphate (PIP3) (Lee et al., 2007).The PI3K are inhibited by the drugs wortmannin and LY294002 although to various degree of sensitivity among the different classes.

Mutations

Somatic

Somatic mutations at the PIK3CA gene have been found in tumors and thus, it can be considered a bona fide oncogene (Samuels et al., 2004). Most of the mutations cluster in hotspots within the helical or the catalytic domains.

Implicated in

A wide variety of human cancers

Note

(For example, colon, breast, endometrial, ovarian, brain, lung, thyroid, head and neck and stomach).

PIK3CA mutations lead to constitutive activation of p110alpha enzymatic activity, stimulate AKT signaling, and allow growth factor-independent growth (Bader et al., 2005). In addition, when expressed in normal cells, these mutations allow anchorage-independent growth, further attesting to their important role in cancer development (Kang et al., 2005). PIK3CA somatic mutations are frequent in a variety of human primary tumors and cancer cell lines such as, among others, those of the colon, breast, and stomach (Samuels et al., 2004). However, in other tumors, i.e. those of the lung, head and neck, brain, endometrium, ovary, prostate, osteosarcoma and pancreas, hematopoietic malignancies, PIK3CA mutations are not as common (Angulo et al., 2008; Qiu et al., 2006; Muller et al., 2007; Samuels et al., 2004; Schonleben et al., 2006). PIK3CA gene amplification has also been proposed as a mechanism for oncogene activation in some tumors (Angulo et al., 2008). Because PIK3CA is now considered an important oncogene implicated in the development of a wide variety of human cancers, efforts are now being directed towards the development of mole-cules that inhibit the activity of PI3K (Garcia-Echeverria et al., 2008). These could be efficient in the treatment of those tumors carrying constitutive activation of PI3K pathway. PTEN is a well known tumor suppressor that counteracts the action of PI3K by dephosphorylating the phosphoinositide-3,4,5-trisphosphate (PIP3). Thus, the treatment with drugs that inhibit p110alpha activity would be also potentially efficient in patients whose tumors carry genetic alterations at PTEN.

It has recently been reported that activation of the PI3K pathway in breast tumors with concomitant ERBB2 gene amplification, either through PIK3CA mutations or PTEN inactivation, underlies trastuzumab resistance. These findings may provide a biomarker to identify patients unlikely to respond to trastuzumab-based therapy (Berns et al., 2007).

To be noted

Note

Recent evidence has shown that the PIK3CA gene is mutated and amplified in a range of human cancers. Due to that p110alpha is believed to be a promising drug target. A number of pharmaceutical companies are currently designing and charactering potential p110alpha isoform specific inhibitors.

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This article should be referenced as such:

Sanchez-Cespedes M. PIK3CA (phosphoinositide-3-kinase, catalytic, alpha polypeptide). Atlas Genet Cytogenet Oncol Haematol. 2010; 14(3):293-295.