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Gene Section
Review

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

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Abstract

Review on PIK3CA, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords
PIK3CA; Kinase; Cell proliferation; Differentiation

Identity

HGNC (Hugo): PIK3CA

Location: 3q26.32

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

Local order: centromere-KCNMB2- ZMAT3-LOC101928739-PIK3CA- KCNMB3- ZNF639-MFN1- GNB4- telomere

DNA/RNA

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.

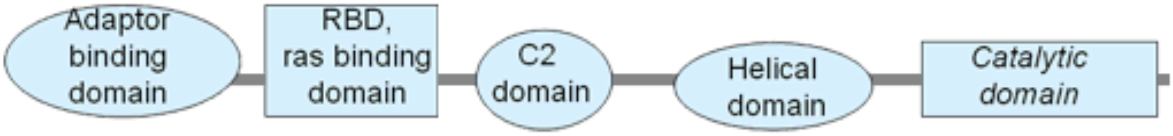
Transcription

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

Pseudogene

A pseudogene has been identified in chromosome 20 (LOC100422375) spanning exons 9 to 13 with 95% homology in both exons and introns.
A non-specific amplification of PIK3CA could result in a E545A false positive mutation which is the amino-acid most commonly mutated in PIK3CA.

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).



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

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.

Function

Class I PI 3-kinases (PI3K) are one of the most prevalently dysregulated pathways in human cancer and it is linked to many cellular functions, including cell growth, proliferation, differentiation, motility, survival and intracellular 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 homology 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. Accordingly, PIK3CA and PTEN genetic alterations are usually alternative events.

Mutations

Somatic

Somatic mutations at the PIK3CA gene have been found in tumors and thus, it is a bona fide oncogene (Samuels et al., 2004). Sequencing analyses of pancancer genomes suggests that PIK3CA has at least 19 mutational hotspots (Chang et al, 2016). Most mutations occur in two of the five domains of p110alpha, the helical and kinase domains. However, while there are no frequent hotspot mutations within the Ras-binding domain (RBD), hotspot mutations within the adaptor-binding domain (ABD) and the C2 domain are also frequently found. Hotspots Arg38 and Arg88 are located within the ABD at the interface with the kinase domain. These mutations disrupt hydrogen bonds between the domains which may alter the conformation of the kinase domain and therefore its enzymatic activity. Similarly, hotspots Asn345 and Glu453 within the C2 domain occur at the interface with the iSH2 domain of p85 and are expected to alter the interaction between these domains. Within the helical domain, the most common hotspots Glu542 and Glu545 are usually mutated into lysine and are located at the interface with the nSH2 domain of p85. A structural model of the p110/niSH2 complex suggests that the contacts between these amino acids and the nSH2 domain occur within a region of the nSH2 domain which is also in contact with the kinase domain of p110. These contacts may serve as the mechanism by which the helical domain mutations alter the activity of the enzyme. In the kinase domain, His1047 is frequently mutated to arginine within a helix at the end of the activation loop. Another less frequent kinase mutation of Met1043 occurs within the same helix and likely has similar effects on enzymatic activity. Thr1025 mutations are located near the N-terminus of the catalytic loop which may directly alter the conformation of the catalytic loop as the mechanism by which the mutation alters enzymatic activity (Huang, 2008). Two other hotspot positions, Lys111 and Gly118, are located outside of the five domains in the 81 residue linker between ABD and RBD (Chang, 2016).

The distribution of PIK3CA hotspot mutations can be significantly variable across tumour types in the kinase and helical domain. For example, cervical and bladder cancers share similar distributions of hotspots but they have far fewer H1047R kinase mutations than breast cancer. Similarly, endometrial and colorectal cancers share distribution patterns but display more R88Q mutations than other tumor types, maybe because this change is a target mutation of POLE genomic instability. However, colorectal cancers differ from endometrial cancers in their clonality. In endometrial tumors, both E545 helical domain mutations and H1047 kinase domain mutations are early clonal mutations whereas in colorectal cancer several E545 mutations are subclonal and H1047 mutations clonal (Chang, 2016).

The variation in hotspot distributions suggests different functions need to be targeted in different tumour types.
Different domain mutations in PIK3CA have been associated with differential signaling. Kinase domain mutations have higher activation of PI3K complexes and increased G-alpha signaling events. However, some components of the G-alpha signaling pathway such as RHO GTPase complexes have lower activity in the kinase domain mutants relative to other PIK3CA mutants. Additionally, helical domain mutations are associated with lower activation of pathways related to proliferation, such as FOXM1, MYC, and PLK1, in comparison to other PIK3CA mutants. The different patterns of pathway activation associated with mutations of specific PIK3CA domains suggest that kinase domain mutations are more strongly associated with proliferation activity, whereas helical domain mutations are more strongly associated with motility activities. These differences in function across domain specific mutations may drive the varying distribution of mutations seen across cancer types (Yau, 2014).

Epigenetics

PIK3CA has a small CpG island in the gene promoter but no methylation has been described.

Implicated in

A wide variety of human cancers

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).

Cowden syndrome

Disease

Syndrome characterized by multiple noncancerous hamartomas and high predisposition to breast, thyroid and other tumour types. Germline PIK3CA mutations may account for around 10% of cases. Most of these mutations are in different positions to main hotspot somatic PIK3CA mutations. Mutations in the genes from the same pathway PTEN and AKT1 may account for about 25% and 2% of cases respectively.

To be noted

Molecular targets: Pan-PI3K inhibitors inhibit all four of the PI3K class I isoforms. However, this broad range of molecular targets results in an increased risk of toxicity and off-target effects. Copanlisib is currently the only pan-PI3K inhibitor that is approved by the FDA for clinical use in treating cancer patients. PI3Kalpha specific inhibitors inhibit the activity of the class I PI3K catalytic subunit alpha isoform and these can be used to target cancers that are dependent on the specific PI3K isoform. The PI3Kalpha isoform is often activated by PIK3CA mutations and initial clinical trials have found greater response to PI3Kalpha inhibitors in PIK3CA mutated cancers than wild type. These specific isoform inhibitors offer greater potential for therapeutic use than nonspecific pan-PI3K inhibitors because they are expected to have fewer off target adverse effects due to the restricted expression of different PI3K isoforms in nonmalignant cells. PI3Kalpha specific inhibitors have yet to be approved for clinical use outside of trials although they have reached the advanced stages of clinical testing (Janku et al, 2018). PI3Kalpha inhibitors seem to result in greater overall response rates and longer progression free survival within patients that possess PIK3CA mutations than without. However, even some patients with PIK3CA mutations have shown short response durations to PI3Kalpha inhibitors (Juric, 2018).
Similarly, aspirin use has been associated with the blocking of the PI3K pathway resulting in suppression of cancer cell growth and induction of apoptosis (Uddin, 2010). A meta-analysis suggests PIK3CA mutations may be predictive of response to aspirin in colorectal cancer although too few studies preclude definitive conclusions (Paleari, 2016). Current trials randomized by aspirin like add-aspirin might be able to validate these findings.

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