

Gene Section

Review

ACVRL1 (activin A receptor type II-like 1)

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Abstract

Activin A receptor, type II-like kinase 1 (ALK1 is a serine-threonine kinase) predominantly expressed on endothelial cells surface. Mutations in its ACVRL1 encoding gene (12q11-14) cause type 2 Hereditary Haemorrhagic Telangiectasia (HHT2), an autosomal dominant multisystem vascular dysplasia. Its involvement in cancer neoangiogenesis has lead to the recent development of novel anti-cancer drugs, which are now in clinical trials.

Identity

Other names: ACVRLK1, ALK-1, ALK1, HHT, HHT2, ORW2, SKR3, TSR-I

HGNC (Hugo): ACVRL1

Location: 12q13.13

DNA/RNA

Note

Starts at 52300692 and ends at 52307134 bp from pter (according to hg19- Feb_2009).

Description

ACVRL1 is a protein coding gene and in human it is constituted by 10 exons. All exons but the first are coding exons. ACVRL1 transcript variants mRNA3 and mRNA4 include 11 exons, through the presence of a cryptic non-translated exon upstream of the canonical exon 1 (Garrido-Martin et al., 2010).

Transcription

Gene database underlines the presence of two different ACVRL1 transcripts, which both translate into the same protein isoform. The second transcript variant is the shortest one and differs from the first one in the 5'UTR region, due to the presence of an upstream in-frame start codon, poorly conserved in the population. Nevertheless, in 2010 two new transcripts were discovered in HUVEC cells. These new variants, called mRNA3 and mRNA4, begin the transcription +1 nucleotide upstream, respectively at -510 and -470 positions, adding a cryptic non translated exon, that doesn't affect the protein ORF (Garrido-Martin et al., 2010).

The promoter region of ACVRL1 (5' proximal region: -1035/+210) was characterized by Garrido-Martin et al., 2010. This region lacks TATA/CAAT boxes but contains a high number of GC-rich Sp1 consensus sites. It also shares different putative regulatory elements with other endothelial-specific genes. These motifs includes: Ets (E26-Transformation-Specific), KLF (Krüppel-Like Factor), NFkB (Nuclear Factor kappa-light-chain-enhancer of activated B cells), E2F (Elongation Factor 2), one Smad binding element (SBE), RXR (Retinoid X Receptor) and HIF (Hypoxia Inducible Factor). Moreover, the authors demonstrated that methylation status of CpG islands modulates Sp1 transcription of ACVRL1 in endothelial cells.

In 2013, it has been demonstrated that ubiquitin E3 ligase, EDD, can down-regulate ACVRL1 expression in HeLa and HUVEC cells (Chien et al., 2013).

Protein

Description

Activin A receptor, type II-like kinase 1 (also called ALK1, Uniprot entry P37023, protein family (pfam) 01064 of Activin types I and II receptor domains), is a serine-threonine kinase and it acts as a type I receptor for the Transforming Growth Factor- β / Bone Morphogenetic Protein (TGF- β /BMP) superfamily of ligands. It includes 503 amino acids, with residues 1-21 forming a leader sequence which targets the protein to the membrane. The extracellular domain includes amino acids 22-118 and it is followed by a 23 amino acid long transmembrane domain (residues 119-141). The intracellular domain comprises residues 142-503, with a GS domain (residues 172-201) and the protein kinase domain (residues 202-492).

The crystal structure of ALK1 ectodomain (Figure 1a) and of the intracellular kinase domain (Figure 1b) have been recently determined (PDB ID: 4FAO and 3MY0, respectively) (Townson et al., 2012).

Like all type I and type II receptors, ALK1 shows a general fold resembling a class of neurotoxins known as three-finger toxins and hence called "three-finger toxin fold". This fold is comprised from β -strands stabilised by disulphide bonds formed by conserved Cys residues. Three pairs of anti-parallel β -strands are curved to generate a concave surface. Despite the common architecture and the cluster of conserved Cys residues, very little sequence identity and no functional overlap exist between the two types of receptors.

BMPs consist of a Cys knot characterised by three pairs of highly conserved disulphide bonds in which one traverses through a ring formed by the other 2. This fold can be described as a hand with a concave palm side and two parallel β -sheet forming 4 fingers, with each β -strand being likened to a finger. Finger 2 leads to a helix "wrist" region. In the dimeric ligand the 4 fingers extend from the Cys core of the protein like butterfly wings. Binding of type I receptors occurs near the α -helix on the concave side at the junction between the two subunits (Kirsch et al., 2000), whereas binding to type II receptors happens on the convex side of the hand near the "fingertips" (Greenwald et al., 2003; Thompson et al., 2003).

Expression

ALK1 is predominantly expressed on the endothelial cells surface of arteries. According to EBI gene expression database, ALK1 levels are reduced in non-small cell lung cancer tissue, and increased in monocytes exposed to infections by *Francisella tularensis novocida* and by *Porphyromonas gingivalis*.

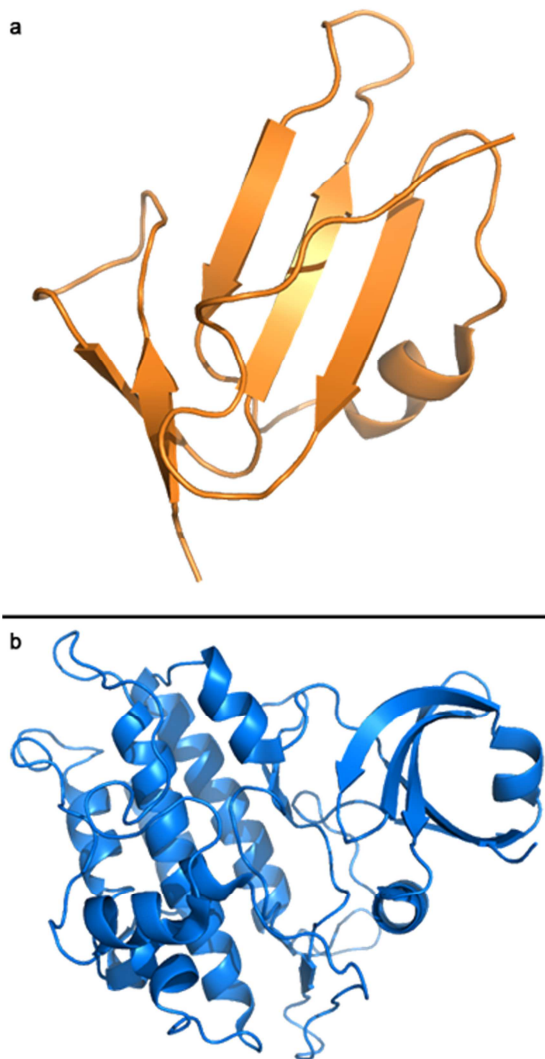


Figure 1: Structures of ALK1 ectodomain (a) and of the kinase domain (b).

Function

ALK1 activation, triggered by its physiological ligand BMP-9, can be pro-angiogenic or anti-angiogenic, depending on the experimental system considered. Thus, inhibition of primary cells (HMVEC-D, HUVEC and endothelial cells) proliferation was observed upon activation of the receptor, suggesting that this signaling pathway is involved in the resolution phase of angiogenesis, during which endothelial cell proliferation and migration stop. Disruption of the pathway would therefore lead to persistent proliferation of endothelial cells with the lack of a correct morphogenesis.

On the other hand, MESEC (mouse embryonic-stem-cell-derived endothelial cells) and MEEC (mouse embryonic endothelial cells) cells are stimulated to proliferate by ALK1 activation and BMP9 stimulates angiogenesis in a matrigel plug assay and in a tumour model in vivo. Also, cancer cells produced tumours whose size and

vascularization were reduced by 50% in ALK1+/- heterozygous mice compared with tumours implanted in wild-type littermates.

In addition, a soluble ALK1-Fc fusion protein known as Dalantercept (ACE-041) showed an anti-angiogenic effect by reducing vascular density and perfusion of the tumour burden in model mice of endocrine pancreatic tumorigenesis and mice bearing 786-0 and A498 human renal cell carcinoma (Wang et al., 2012).

This contradictory findings may be explained by the site- and context-dependent balance of the synergic proangiogenic effects of BMP-9 and the lower affinity ALK1 ligand TGF- β , but the assumption has to be confirmed.

Recent studies also report a role for ALK1 in cancer independent from its effects on angiogenesis, enhancing the cell migration and invasion potential in cancers like squamous cell carcinomas of the head and the neck or hepatocarcinomas (Hu-Lowe et al., 2011; Chien et al., 2013; Sun et al., 2013).

ALK1 signalling through SMAD 1/SMAD 5/SMAD 8 seems to induce chondrocytes hypertrophy in cartilages by an effect mediated by the interaction with the canonical Wnt signaling (van den Bosch et al., 2014).

Again, in other kind of cancers ALK1 activation seems to be protective, as assessed for instance in in vitro models of pancreatic cancers (Ungefroren et al., 2007).

Homology

ALK1 shares with other type I receptors a high degree of similarity in the GS domain, in the following serine-threonine kinase subdomains and in the short C-terminal tail (ten Dijke et al., 1994), but the extracellular domain shows a peculiar amino acidic sequence.

Mutations

Germinal

Mutations in the ACVRL1 gene result in Hereditary Hemorrhagic Telangiectasia Type 2 (HHT2). A germinal mosaic with two mutant alleles in hereditary hemorrhagic telangiectasia associated with pulmonary arterial hypertension was described (Eyries et al., 2011).

A germline heterozygous ACVRL1 polymorphisms (p. A482V) has been reported in a patient with a gonadotroph pituitary tumour by D'Abronzio et al., 1999.

Somatic

No somatic mutations of ACVRL1 have been found in human cancers.

Implicated in

Solid tumours

Note

As a receptor mainly expressed on the surface of endothelial cells, ALK1 overexpression and unbalances in its signalling are implicated in many solid tumours, despite the origin and specific features of the latter. Thus, they will be discussed in a single paragraph.

In a study (Hu-Lowe et al., 2011) performed on 3000 human tumour specimens representing more than 100 tumour types, ALK1 resulted particularly expressed in the vasculature of prostate cancers, malignant melanomas of the skin, follicular cancers of the thyroid, renal clear cell cancers and endometrioid ovarian cancers.

A reduced expression of ACVRL1 by qRT-PCR and immunohistochemistry was demonstrated in nasopharyngeal carcinomas by Zhang et al., 2012.

An increased ALK1 expression in papillary thyroid carcinomas with bone formation was increased if compared to that in normal thyroid tissue and tumors without bone formation, as assessed using immunohistochemistry and quantitative real-time polymerase chain reaction (Na et al., 2013).

In Head and Neck Squamous Cell Carcinomas (HNSCC), using immunohistochemistry and qRT-PCR, Chien et al. found a correlation between a high ACVRL1 expression and an advanced T classification, a positive N classification, an advanced TNM stage, the presence of lymphovascular invasion, an extracapsular spread of lymph node metastasis and a poorer prognosis (Chien et al., 2013).

As a therapeutic target, anti-ALK1 drugs (both in the form of an Fc-fusion protein acting as a soluble receptor for BMP9 and of an anti-ALK1 monoclonal antibody) are under investigation in phase I and phase II clinical trials in a wide range of solid tumours (Vecchia et al., 2013). Phase II studies clinical trials encompass particularly squamous cell carcinoma of the head and neck, endometrial cancer, epithelial ovarian cancer, fallopian tube cancer and primary peritoneal carcinoma for ACE-041 (also known as Dalantercept, the Fc-receptor fusion protein). Dalantercept displayed promising antitumour activity particularly in patients with advanced refractory cancer (Bendell et al., 2014). PF-03446962 (the anti-ALK1 monoclonal antibody), is up to now studied in phase II clinical trials particularly in malignant mesotheliomas of the pleura and transitional cell carcinomas of the bladder.

A recent study showed that PF-03446962 has no activity as a single drug in refractory urothelial cancer as is thus suggested, for this kind of cancer, only as a combination therapy with other agents against the VEGF receptor axis (Necchi et al., 2014). Both Dalantercept and PF-03446962 are currently under investigation in phase II trials particularly in advanced and refractory hepatocarcinomas.

As assessed by Hosman et al., 2013, mutations in ACVRL1 gene, as the ones observed in HHT2 patients, seem to reduce the prevalence of some types of solid tumours and account for the unexpected good life expectancy of HHT patients older than 60 years of age.

Although it is important to take with care the results of the study due to the methodology used for the assessment (for the statistical and logistic difficulties to perform a longitudinal study in a rare disease, the authors used a questionnaire, inevitably biased), HHT patients older than 60 presented an apparent reduction in lung, liver and colorectal cancer compared to controls.

This could potentially be related to the ALK1 haploinsufficiency present in ALK1 HHT mutations, opposite to the overexpression usually showed in cancers.

On the other hand, colorectal cancer was instead more frequent in younger HHT patients, particularly in the subgroup with SMAD4 mutations and juvenile polyposis.

Hereditary hemorrhagic telangiectasia type 2 (HHT2)

Note

Hereditary Hemorrhagic Telangiectasia (HHT), or Rendu-Osler-Weber disease, is a vascular dysplasia inherited as an autosomal dominant trait (Shovlin, 2010; McDonald et al., 2011). It affects approximately 1 in 5-8000 individuals (Faughnan et al., 2011) with regional differences due to founder effects (Westermann et al., 2003; Lesca et al., 2008). The clinical diagnosis of HHT is based on the presence of at least three of the following "Curaçao criteria" (Shovlin et al., 2000): (1) spontaneous, recurrent epistaxis; (2) mucocutaneous telangiectases at characteristic sites as nose, lips, oral cavity, finger tips and gastrointestinal (GI) mucosa; (3) visceral arteriovenous malformations (AVMs) in lungs, liver, GI, brain and spinal cord; (4) family history of first-degree relative in whom HHT has been diagnosed using these criteria. Significant clinical variability was observed in HHT (Lesca et al., 2007; Govani and Shovlin, 2009), with both intra- and interfamilial variations in age-of-onset, localization of lesions, and severity of complications, whereas it usually shows a high

penetrance. HHT is usually not apparent at birth, but evolves with age into a recognizable phenotypic pattern. Spontaneous recurrent nosebleeds are the most common and usually earliest clinical manifestation. HHT telangiectases develop and get worse with age. Complete penetrance was found to be by 40 years of age (Porteous et al., 1992). HHT patients show approximately 15-50% of pulmonary AVMs (PAVMs), 32-78% of liver AVMs (HAVMs) and approximately 23% will harbor AVMs in the brain (CAVMs). Although 80% of patients with HHT have gastric or small intestinal telangiectases, only 25-30% of patients will develop symptomatic GI bleeding which usually does not present until the fifth or sixth decades of life (Faughnan et al., 2011).

HHT arises from heterozygous mutations in ENG (HHT1, OMIM #187300) coding for ENDOGLIN (ENG) (McAllister et al., 1994) and ACVRL1 (HHT2, OMIM #600376) coding for ALK1 (Johnson et al., 1996), Type III and Type I TGF- β receptors, respectively. Certain HHT2 patients develop a Pulmonary Artery Hypertension (PAH)-like syndrome, suggesting that ACVRL1 mutations are also likely to be involved in PAH (Trembath et al., 2001; Olivieri et al., 2006). A subset of patients with juvenile polyposis, carrying mutations in SMAD4/MADH4 (JPHT, OMIM #175050), can also develop HHT (Gallione et al., 2004). Recently, mutations in BMP9 were reported in three unrelated families affected by a vascular-anomaly syndrome presenting with phenotypic overlap with HHT (Wooderchak-Donahue et al., 2013). Additional as-yet-unknown HHT genes have been suggested by linkage analysis in two affected kindred on chromosome 5 and on chromosome 7 (Cole et al., 2005; Bayrak-Toydemir et al., 2006). Molecular genetic testing of the three known genes detects mutations in approximately 85% of patients. As reported above, the mutated genes encode proteins that mediate signaling by TGF- β family.

More than 375 ACVRL1 variants are present in the international HHT mutation database and more than 185 are demonstrated to be pathogenic for HHT.

TGF- β ligands regulate angiogenesis through their actions either on endothelial cells (EC) and/or mural cell, demonstrating that they play important roles in both activation (via ALK1) and resolution (via ALK5) phases of angiogenesis. It has been reported that BMP9, rather than BMP10, might be the specific ALK1 ligand and activator of the Smad1/5/8 signaling pathway in endothelial cells and that they are potent inhibitors of EC migration and growth (David et al., 2007). Previous studies have suggested the synergy between Notch and TGF- β , and that Notch signaling modulates the balance between TGF- β /ALK1 and TGF- β /ALK5 signaling pathways (Fu et al., 2009).

ALK1-1 and pulmonary arterial hypertension

Note

Pulmonary arterial hypertension (PAH) is a severe and rare disease affecting small pulmonary arteries, with progressive remodeling leading to elevated pulmonary vascular resistance and right ventricular failure, and is a major cause of progressive right-sided heart failure and premature death (Trembath et al., 2001). PAH is defined as the sustained elevation of mean pulmonary artery pressure (PA) above 25 mmHg at rest or 30 mmHg during exercise (Rabinovitch, 2012). The histopathology is marked by vascular proliferation/fibrosis, remodeling, and vessel obstruction (Chan and Loscalzo, 2008).

In the second World Symposium held in Evian, France, in 1998, was proposed a clinical classification for pulmonary hypertension. The first category was defined PAH and includes two subgroups, the first incorporates both the idiopathic form (IPAH) that the inherited (HPAH) of the disease. The second subgroup includes a number of conditions associated with various diseases (APAH), including connective tissue diseases, human immunodeficiency virus infection, congenital heart disease, and portal hypertension (Simonneau et al., 2004; Machado et al., 2009).

Heterozygous mutations in the transforming growth factor- β receptor (TGF- β receptor) super family have been genetically linked to PAH and likely play a causative role in the development of disease. Particularly, mutations in the bone morphogenetic factor receptor type 2 (BMPR2) gene account for approximately 70% of all familial pedigrees of PAH (HPAH) and 10-30% of idiopathic PAH cases (IPAH) (Chan and Loscalzo, 2008; Machado et al., 2009).

Much less commonly (5%) two other members of the TGF- β superfamily are also recognized as uncommon causes of PAH: activin A receptor type II-like kinase 1 (ALK1) and, at significant lower frequency, endoglin (ENG) (Harrison et al., 2003). Heterozygous mutations of these genes cause the autosomal dominant vascular disorder hereditary haemorrhagic teleangiectasia (HHT) (Shovlin, 2010). In fact, in a small proportion of HHT patients, was observed a form of pulmonary arterial hypertension that is associated with a model of precapillary pulmonary hypertension that is histopathologically indistinguishable from idiopathic form of PAH. Since the publication by Trembath et al. in 2001 (Trembath et al., 2001), who first reported patients with a mutation in the gene ACVRL1 with clinical features of both PAH and HHT, subsequently, have been recognized several other mutations in the ALK1 gene that seem to predispose patients with HHT development of

PAH. This observation was further confirmed by other studies (Olivieri et al., 2006) and extensively discussed by Machado et al. (Machado et al., 2009). The exact prevalence of PAH in the HHT population has not been systematically evaluated, but most authors agree that it is a rare complication found in less than 1% of HHT patients (Cottin et al., 2007). In rare cases, ACVRL1 mutations have been reported to cause IPAH or HPAH without HHT (Harrison et al., 2003).

Both ALK1 and BMPR2 belong to the family of TGF- β receptors, they have different specific ligands but share a common intracellular pathway based on the activation of the SMAD proteins 1/5/8 (Faughnan et al., 2009).

The formation of an heteromeric complex with BMPR2 and ALK1 could at least in part explain why any dysregulation of this pathway may promote pulmonary endothelial and/or smooth muscle cell dysfunction and proliferative characteristic of PAH, in subjects carrying mutation either in BMPR2 or in ACVRL1 gene.

Mutations identified in several studies on ALK1 associated with PAH are all likely to disrupt activation of this intracellular pathway and the majority of these comprise missense mutations. Particularly, mutations in exon 10 of ACVRL1 are relevant because they occur in functional domains of the receptor within a conserved carboxyl-terminal region of ALK1 (the non-activating non-down regulating box) NANDOR BOX (Faughnan et al., 2009; Machado et al., 2009).

Of note, the NANDOR BOX, located from codon 479 to 489, is necessary for regulation of TGF- β signaling, accordingly any alteration may have effects on TGF- β -induced receptor signaling (Girerd et al., 2010).

Moreover, recent studies in animal models have shown that Alk1 heterozygous mice spontaneously develop signs of pulmonary hypertension in the early months of life, and with increasing age show more occluded vessels and pulmonary vascular remodeling, indicating a progression of the disease. These mice had also higher ROS levels in adult lungs contributing to PAH development compared to control mice.

Whereas Bmpr2 heterozygous mouse model requires additional factors, such as hypoxia and serotonin or inflammation, to elicit a pulmonary hypertensive phenotype (Jerkic et al., 2011).

Finally, Girerd B. et al. hypothesized that mutated ACVRL1 status might be associated with distinct PAH phenotypes, as compared with patients PAH without ALK1 mutations.

The authors analyzed clinical, functional characteristic, hemodynamic features and outcomes for patients with PAH carrying ACVRL1 mutation. Of notice, these patients were significantly younger at diagnosis (P

Pulmonary arterial hypertension is therefore a complex disease that involves the interaction between genetic predisposition and environmental risk factors. The identification of human mutations in components of the TGF- β receptor different from each other but somehow bound by common intracellular signaling pathways, which may lead to the development of pulmonary vascular disease, has provided important targets for further investigation.

Hematological malignancies

Note

Roughly 80% of non-Hodgkin's lymphomas and 60% of Hodgkin lymphomas express ALK1 in their vasculature (Hu-Lowe et al., 2011). The expression of ALK1 in haematological cancers was further confirmed in an exploratory study on patients affected with Acute Myeloid leukemia (AML) (Otten et al., 2011).

Using qRT-PCR, ALK1 was demonstrated to be expressed by 82% of patients' samples (pretherapeutic bone marrow or peripheral blood from 93 patients with newly diagnosed AML). Furthermore, formalin-fixed, paraffin-embedded trephine bone marrow specimens from two arbitrarily selected patients with AML and from two patients with non-leukemic reactive changes were analyzed for ALK-1 expressions by immunohistochemistry. Endothelial cells from two AML patients and those with reactive disorders were strongly positive and a fraction of AML blasts stained positively for ALK-1 in AML bone marrows, whereas normal hematopoietic cells were negative.

Anyway, ALK1 alterations, opposite to those in ALK5, seemed not to have a significant impact on survival. Furthermore, the prevalence of haematological cancers in HHT patients as assessed by Hosman et al., 2013 showed no difference compared to controls.

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