Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

EPHA3 (EPH receptor A3)

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Published in Atlas Database: April 2009

Online updated version: http://AtlasGeneticsOncology.org/Genes/EPHA3ID40463ch3p11.html
DOI: 10.4267/2042/44710

Identity

Other names: EC 2.7.10.1; ETK; ETK1; EphA3; HEK; HEK4; TYRO4

HGNC (Hugo): EPHA3

Location: 3p11.2

Local order: (tel) C3orf38 (ENSG00000179021) ->, 949,562bp, EPHA3 (374,609bp) ->, 720,071bp, <- AC139337.5 (ENSG00000189002) (cen)

Note
EPHA3 is flanked by two gene deserts.

DNA/RNA

Note
EPHA3 spans the human tile path clones CTD-2532M17, RP11-784B9 and RP11-547K2.

Description

EPHA3 consists of 17 exons and 16 introns and spans 375kb of genomic DNA. It is the second largest of the EPH genes after EPHA6.

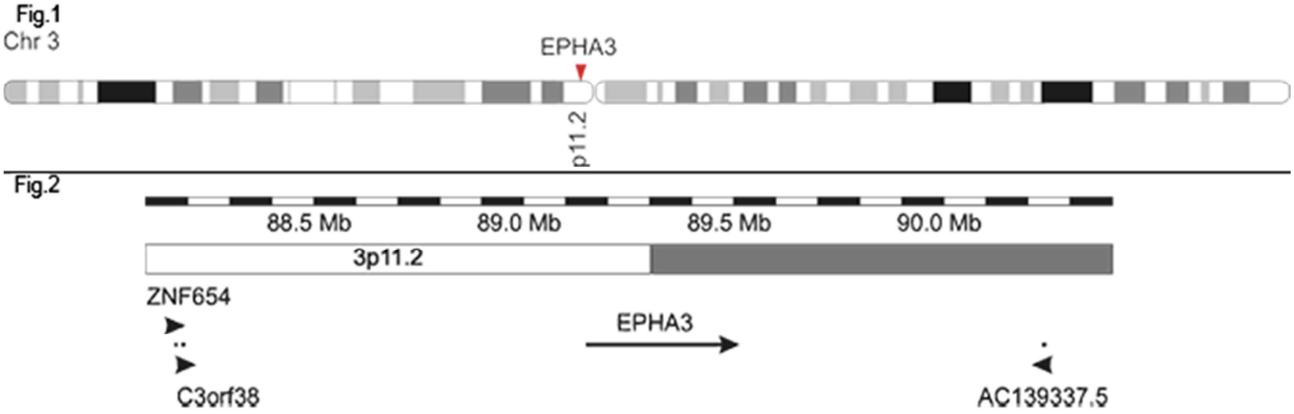


Figure 1: Chromosomal location of EPHA3 (based on Ensembl Homo sapiens version 53.36o (NCBI36)).
Figure 2: Genomic neighbourhood of EPHA3 (based on Ensembl Homo sapiens version 53.36o (NCBI36)).

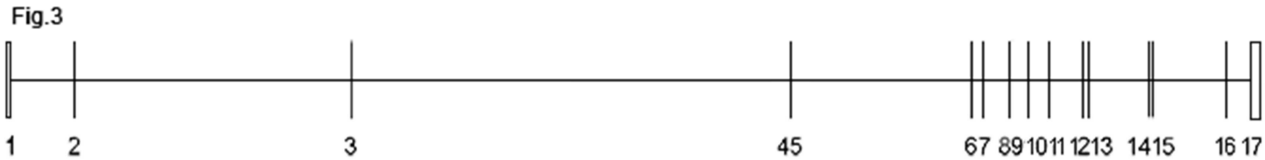


Figure 3: Genomic organisation of EPHA3.

Transcription

Two alternatively spliced transcript variants have been described (NM_005233.5, a 5,807 nucleotide mRNA and NM_182644.2, a 2,684 nucleotide mRNA). The shorter transcript results in truncation within the extracellular domain of EphA3 and is predicted to produce a soluble protein. The 5' end of EPHA3 is associated with a CpG island, a feature common to all EPH genes. The EPHA3 promoter also lacks a TATA box and transcription initiates from multiple start sites.

Pseudogene

None identified.

Protein

Note

The Eph receptors constitute the largest of the 20 subfamilies of human receptor tyrosine kinases. The founding member of this group was isolated originally from an erythropoietin producing hepato-ma cell line.

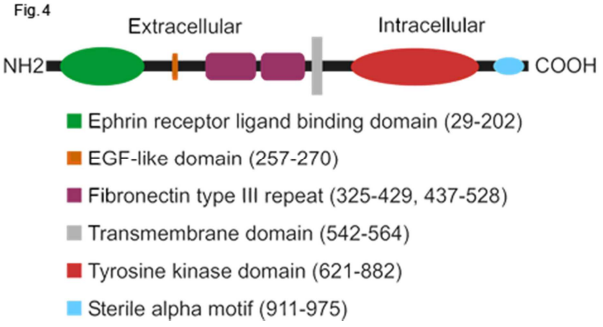


Figure 4: Domain organisation of EphA3.

Description

The EPHA3 gene encodes a 983 amino acid protein with a calculated molecular weight of 110.1kDa and an isoelectric point of 6.7302. Amino acids 1-20 constitute a signal peptide. The predicted mole-cular mass of the translated protein minus the signal peptide is 92.8kDa. The 521 amino acid extra-cellular domain contains five potential sites for N-glycosylation such that EphA3 is typically detected as a 135kDa glycoprotein. This mature isoform of EphA3 is a single-pass transmembrane receptor tyrosine kinase. At its N-terminus is a 174 amino acid ligand binding domain, a 14 amino acid EGF-like domain and two membrane proximal fibro-nectin type III repeats. Amino acids 21-376 of the extracellular domain also are rich in cysteine residues. The intracellular domain contains the tyrosine kinase domain and a sterile alpha motif. EphA3 lacks a PDZ domain interacting motif present in EphA7, EphB2, EphB3, EphB5 and EphB6. Activation of the EphA3 receptor tyrosine kinase domain is associated with two tyrosine residues in the juxtamembrane region (Y596, Y602) that are sites of autophosphorylation and interact with the kinase domain to modulate its activity.

EphA3 belongs to an evolutionarily ancient subfamily of receptor tyrosine kinases with mem-bers being present in sponges, worms and fruit flies. The expansion in the number of Eph receptor-encoding genes along with genes encoding their ligands, the ephrins (Eph receptor interacting proteins), is proposed to have contributed to the increase in complexity of the bilaterian body plan. Genes encoding EphA3 are found in the genomes of representative members of at least five of the seven classes of vertebrates including bony fish (zebrafish, pufferfish, medaka), amphibians (African clawed frog), reptiles (green anole lizard), birds (chicken) and mammals (platypus, possum, human).

Fourteen Eph receptors have been identified in vertebrates. These are subdivided into either EphA (EphA1, EphA2, EphA3, EphA4, EphA5, EphA6, EphA7, EphA8, EphA10) or EphB (EphB1, EphB2, EphB3, EphB4, EphB6) subclasses which differ primarily in the structure of their ligand binding domains. EphA receptors also exhibit greater affinity for binding GPI-linked ephrin-A ligands while EphB receptors bind transmembrane ephrin-B ligands. While interactions are somewhat promis-cuous, and some cross-class binding occurs, each Eph receptor displays distinct affinity for the different ephrin ligands. The high affinity ligands for EphA3 are ephrin-A2 and ephrin-A5. EphA3 also binds ephrin-A3 and ephrin-A4 with lower affinity.

Eph-ephrin binding involves contact between cells. Upon binding, receptor-ligand dimers form heterotetramers, which further assemble into higher order signalling clusters. Several moieties in the EphA3 receptor extracellular region mediate ephrin binding. A high-affinity binding site in the N-terminal ephrin binding domain mediates inter-cellular Eph-ephrin interaction. Two additional lower-affinity ephrin-binding sites, one in the ephrin-binding domain and the other in the cysteine-rich region, are involved in clustering of Eph-ephrin complexes.

Following ephrin-A5-mediated EphA3 receptor clustering, intracellular signalling by EphA3 receptors is initiated by autophosphorylation of three defined tyrosine residues, two in the highly conserved juxtamembrane region and the third in the activation loop of the kinase domain (Y779). Rapid reorganisation of the actin and myosin cytoskeleton follows, leading to retraction of cellular protrusions, membrane blebbing and cell detachment, following association of the adaptor protein CrkII with tyrosine phosphorylated EphA3 and activation of RhoA signalling.

Such Eph-ephrin interaction triggers bidirectional signalling, that is signalling events within both Eph- and ephrin-bearing cells, an unusual phenomenon for receptor tyrosine kinases, most of which interact with soluble ligands. Subsequently, depending on the cellular context (including the identity of the interacting Eph-ephrin receptor-ligand pairs, their relative levels on interacting cells, the presence of additional Ephs and ephrins and their alternative

isoforms, and the net effect of interaction with additional signalling pathways) this either results in repulsion or promotes adhesion of the interacting cells.
Cellular repulsion and the termination of Eph-ephrin signalling require disruption of the receptor-ligand complex. This is brought about either by enzymatic cleavage of the tethered ephrin ligand in cis or in trans or by endocytosis of Eph-ephrin complexes. EphA3-ephrin-A2 receptor-ligand complexes are shed from ephrin-A2 bearing cells following receptor-ligand binding when ADAM10 (a disintegrin and metalloprotease 10), associated with ephrin-A2, cleaves ephrin-A2. Conversely, intercellular EphA3-ephrin-A5 receptor-ligand complexes are broken when EphA3-associated ADAM10 cleaves ephrin-A5 on opposing cells, following binding to EphA3. The post-cleavage ephrin-A5-EphA3 complex is then endocytosed by the EphA3-expressing cell.
While cellular repulsion is often the outcome of Eph-ephrin interaction, in some circumstances adhesion may persist. For example, ADAM10 has been observed not to cleave ephrin-A5 following EphA3-ephrin-A5 interaction involving LK63 cells in which high intracellular protein tyrosine phosphatase activity also appears to counter ephrin-A5 stimulated phosphorylation of EphA3, holding the receptor in an inactive, unphosphorylated state. Also cis interaction between EphA3 and ephrin-A2 expressed on the same cell surface has been reported to block EphA3 activation by ephrins acting in trans, the cis interaction site being independent of the ligand binding domain. Another mechanism that may favour stable cell-cell adhesion involves truncated Eph receptor isoforms acting in a dominant negative manner. While activation of full length EphA7 by ephrin-A5 results in cellular repulsion, ephrin-A5-induced phosphorylation of EphA7 is inhibited by two EphA7 splice variants with truncated kinase domains and adhesion results. A splice variant of EPHA3 also has been reported and is predicted to give rise to a soluble isoform of EphA3. Whether this soluble variant of EphA3, which is truncated before the transmembrane domain, functions in a similar manner to the shorter EphA7 isoforms has not been established.
While important details of EphA3 signalling have been determined, more complete understanding of EphA3 activity will require knowledge of the full complement of EphA3 interacting proteins. Substrates that are targets for the tyrosine kinase activity of EphA3 have yet to be defined and potential mediators or modulators of EphA3 signalling output such as Src family kinases, additional phosphotyrosine binding adaptors, SAM domain interacting factors, interaction with other receptor kinases and crosstalk with other signalling pathways, and the regulatory role of phosphatases all remain to be explored. Based on the range of interacting proteins identified for other Eph receptors (some common to more than one Eph, others apparently unique to individual Ephs) additional effectors of EphA3 signalling output are likely.

Expression

EphA3 was first identified as an antigen expressed at high levels (10,000-20,000 copies per cell) on the surface of the LK63 pre-B cell acute lymphoblastic leukaemia cell line. It also was found to be expressed by JM, HSB-2 and MOLT-4 T-cell leukaemic cell lines, in CD28-stimulated Jurkat cells, and in 16 of 42 cases of primary T-cell lymphoma (but not normal peripheral T lymphocytes nor in any subset of thymus-derived developing T cells), as well as at low frequency in acute myeloid leukaemia and chronic lymphocytic leukaemia EphA3 is not expressed by many other haematopoietic cell lines.
Subsequently, EphA3 expression has been shown to be most abundant, and also highly regulated both temporally and spatially, during vertebrate development. Prominent EphA3 expression occurs in the neural system, including the retinal ganglion cells of the embryonic retina in a graded distribution from anterior/nasal (lowest) to posterior /temporal (highest); the cerebrum, thalamus, striatum, olfactory bulb, anterior commissure, and corpus callosum of the forebrain; and the medial motor column ventral motor neurons of the spinal cord; and extraneurally by mesodermally-derived tissues including the paraxial musculature, tongue musculature, submucosa of the soft palate, capsule of the submandibular gland, cortical rim of bone, thymic septae, media of the pharynx, trachea, great vessels, small intestine and portal vein, cardiac valves, and the renal medulla. In adult tissues EphA3 expression is more restricted and detected at significantly lower levels than during early development.

Localisation

Isoform 1: Cell membrane; single-pass type I membrane protein.
Isoform 2: Secreted.

Function

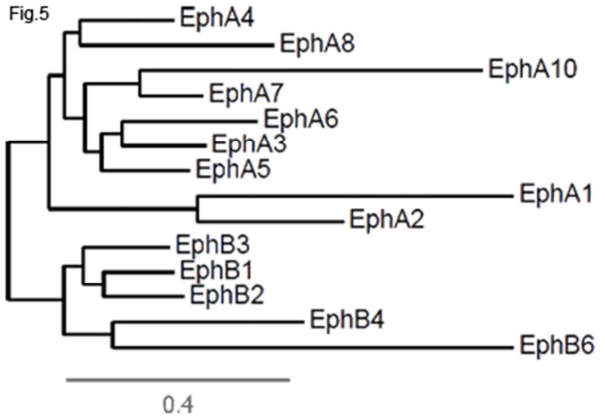
Eph receptors modulate cell shape and movement through reorganisation of the cytoskeleton and changes in cell-cell and cell-substrate adhesion, and are involved in many cellular migration, sorting (tissue patterning) and guidance events, most often during development, and in particular involving the nervous system. There is evidence too that Eph receptor signalling influences cell proliferation and cell-fate determination and growing recognition that Eph receptors function in adult tissue homeostasis.
EphA3 is thought to play a role in retinotectal mapping, the tightly patterned projection of retinal ganglion cell axons from the retina to the optic tectum (or superior colliculus in mammals). In chicks, posterior retinal ganglion axons expressing highest levels of EphA3 project to the anterior tectum where the graded

expression of ephrin-A2 and ephrin-A5 is lowest and are excluded from projecting more posteriorly where ephrin-A2/A5 expression is highest. More direct evidence of non-redundant function for EphA3 has come from phenotypic analysis of EphA3 knockout mice. Approximately 70-75% of EphA3 null mice die within 48 hours of birth with post-mortem evidence of pulmonary oedema secondary to cardiac failure. These mice exhibit hypoplastic atrioventricular endocardial cushions and subsequent atri-oventricular valve and atrial membranous septal defects, with endocardial cushion explants from these mice giving rise to fewer migrating cells arising from epithelial to mesenchymal trans-formation. Expression of EphA3 in the spinal cord appears to be redundant as axial muscle targeting by medial motor column motor axons and the organisation of the motor neuron columns is not altered. EphA4 is the only other EphA receptor also expressed by developing spinal cord motor neurons and in mice lacking EphA3 and EphA4 these receptors together repel axial motor axons from neighbouring ephrin-A-expressing sensory axons, inhibiting intermingling of motor and sensory axons and preventing mis-projection of motor axons into the dorsal root ganglia. In contrast to the chick, EphA3 is not expressed by mouse retinal ganglion cells. Instead the closely related receptors EphA5 and EphA6 (see homology below) are expressed in a low nasal to high temporal gradient. However, if EphA3 is ectopically expressed in retinal ganglion cells in mice these axons project to more rostral positions in the superior colliculus.

A function for soluble EphA3 has not been reported although potentially this isoform might play a role in promoting cell adhesion (see above) or act as a tumour suppressor protein (see below).

Homology

Phylogenetic tree for the Eph receptors. Amino acid sequences used for this compilation were EphA1 (NP_005223), EphA2 (NM_004431), EphA3 (NP_005224), EphA4 (NP_004429), EphA5 (NM_004439), EphA6 (ENSP00000374323), EphA7 (NP_004431), EphA8 (NP_065387), EphA10 (NP_001092909), EphB1 (NP_004432), EphB2 (NP_004433), EphB3 (NP_004434), EphB4 (NP_004435) and EphB6 (NP_004436).



Mutations

Note

Seven nonsynonymous single nucleotide polymerphisms (all missense) are recorded in the dbSNP database for EPHA3. Recognised allelic variation occurs for the following EphA3 amino acids: I564V (rs56081642), C568S (rs56077781), L590P (rs56081642), T608A (rs17855794), G777A (rs34437982), W924R (rs35124509) and H914R (rs17801309).

Germinal

To date no germinal mutations in EPHA3 have been associated with disease.

Somatic

Somatic mutations in EPHA3 have been detected in lung adenocarcinoma (T166N, G187R, S229Y, W250R, M269I, N379K, T393K, A435S, D446Y,

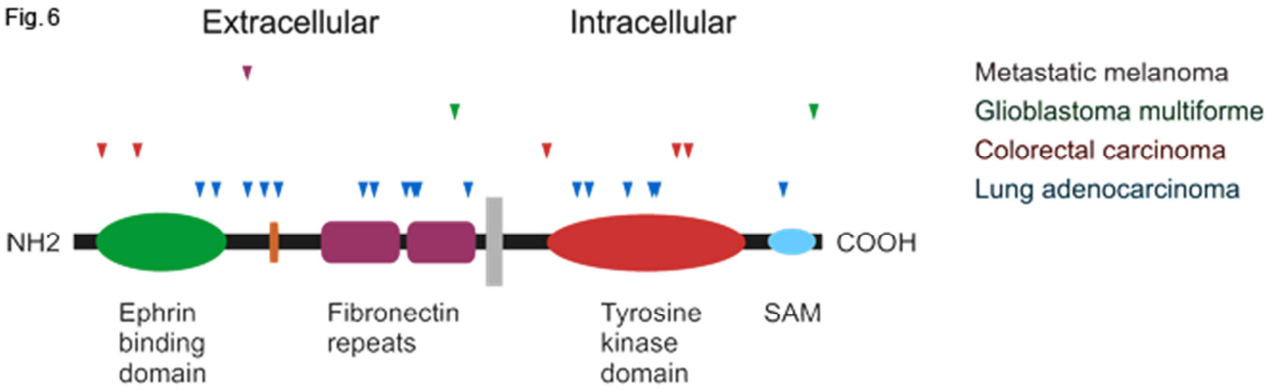


Figure 6: Sites of somatic mutations in EphA3 identified in lung adenocarcinoma colorectal carcinoma, glioblastoma multiforme and metastatic melanoma.

S449F, G518L, T660K, D678E, R728L, K761N, G766E, T933M), colorectal carcinoma (T37K, N85S, I621L, S792P, D806N), glioblastoma multi-forme (K500N, A971P) and metastatic melanoma (G228R).

Implicated in

Prostate cancer

Note

EPHA3 was among the genes whose expression was upregulated during androgen-independent progresssion in an LNCaP in vitro cell model of prostate cancer.

Melanoma

Note

A melanoma patient with an especially favourable evolution of disease, associated with a very strong and sustained anti-tumour cytotoxic T lymphocyte response, was found to have a lytic CD4 clone that recognised an EphA3 antigen presented by the HLA class II molecule HLA- DRB1*1101. 94% (75 of 80) of melanomas examined expressed EphA3 in contrast to normal melanocytes which do not express detectable EphA3.

Lung cancer, Sarcoma, and Renal cell carcinoma

Note

44% (11 of 25) of small cell lung cancer, 24% (10 of 41) of non-small cell lung cancer, 58% (17 of 29) of sarcomas, and 31% (12 of 38) of renal cell carcinomas expressed EphA3 at levels significantly higher than the corresponding normal tissues.

Breakpoints

Note

No reported breakpoints identified to date nor recognised fusion proteins involving EphA3.

To be noted

Note

Soluble forms of EphA3 appear to inhibit tumour angiogenesis and tumour progression suggesting that specific inhibition by soluble EphA3 may be therapeutically useful.

The IIIA4 monoclonal antibody originally raised against LK63 human acute pre-B leukemia cells and used to affinity isolate EphA3 binds the native EphA3 globular ephrin-binding domain with sub-nanomolar affinity (KD ~$5x10^{-10}$ mol/L). Like ephrin-A5, pre-clustered IIIA4 effectively triggers EphA3 activation, contraction of the cytoskeleton, and cell rounding. Moreover, radio-metal conju-gates of ephrin-A5 and IIIA4 retain their EphA3-binding affinity, and in mouse xenografts localise to, and are internalised rapidly into EphA3-positive, human tumours.

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This article should be referenced as such:

Stringer B, Day B, McCarron J, Lackmann M, Boyd A. EPHA3 (EPH receptor A3). Atlas Genet Cytogenet Oncol Haematol. 2010; 14(3):279-285.