Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section
Review

TEK (TEK tyrosine kinase, endothelial)

Mohammad B Hossain, Nahir Cortes-Santiago, Dan Liu, Vanesa Martin, Candelaria Gomez-Manzano

Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA (MBH, NCS, DL, VM), Departments of Neuro-Oncology and of Genetics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA (CGM)

Published in Atlas Database: April 2012

Online updated version : http://AtlasGeneticsOncology.org/Genes/TEKID42517ch9p21.html
DOI: 10.4267/2042/47539

This article is an update of :
Liu D, Martin V, Gomez-Manzano C. TEK (TEK tyrosine kinase, endothelial). Atlas Genet Cytogenet Oncol Haematol 2009;13(12):975-977.

Identity

Other names: CD202B, CD202b, EC 2.7.10.1, hTIE2, p140 TEK, TIE-2, TIE2, VMCM, VMCM1

HGNC (Hugo): TEK

Location: 9p21.2

Note: Tie1 and Tie2 [where 'Tie' is an acronym from tyrosine kinase with Ig and EGF homology domains] are the two members of the Tie family of tyrosine kinase receptors. Tie2 has highly conserved sequence across vertebrate species, with greatest amino acid homology occurring in the kinase domain, predominantly express on the surface of endothelial cells. Three secreted natural ligands have been characterized, - Ang1, Ang2 and interspecies orthologs Ang3 (mouse) and Ang4 (human).

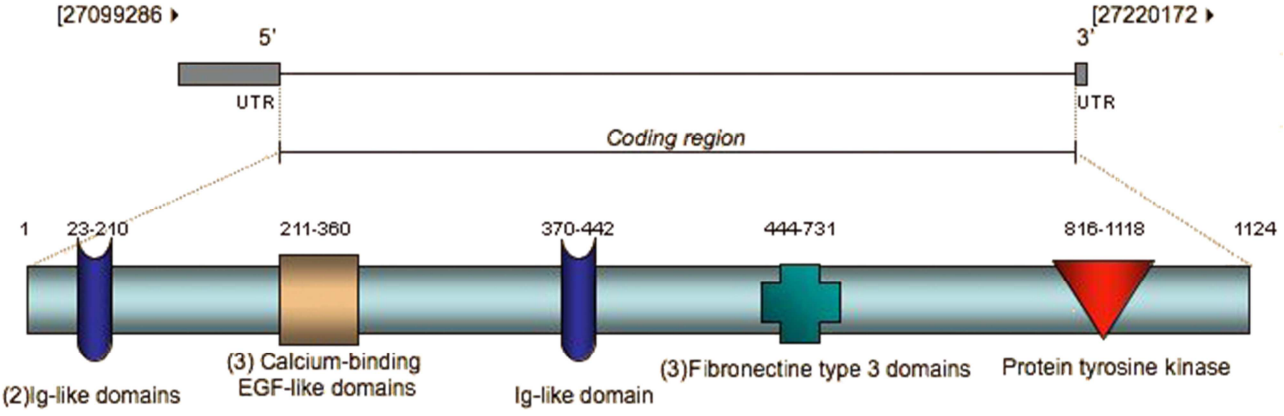
DNA/RNA

Description

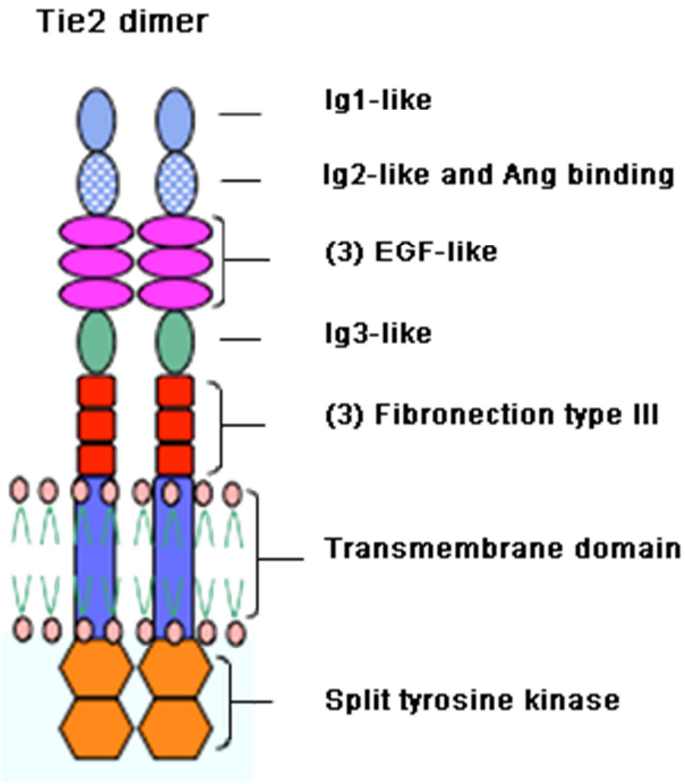
Tie2 DNA contains 121025 bp, which has 23 coding exons, in plus strand.

Transcription

mRNA contains 4817 bp transcribed in centromeric to telomeric orientation; 2 other transcripture structures by alternative splicing have been predicted. The mRNA contains a long (442 bp) 5'-UTR with 5 upstream ORFs and 1 IRES that allows the RNA to be translated under hypoxic conditions.



Schematic representation of TEK gene, coding region and protein. UTR, untranslated region; Ig, immunoglobulin; EGF, epithelial growth factor.



Protein

Description

Tie2 contains 1124 amino acids and belongs to the protein kinase superfamily, Tyr protein kinase family, Tie subfamily. Tie2 receptor contains three epidermal growth factor (EGF)-like domains flanked by three Ig-like (immunoglobulin-like) domains, followed by three fibronectin type-III domains in the extracellular domain. Tie2 possesses one intracellular split tyrosine kinase domain, which is highly conserved between the Tie members sharing a 76% sequence homology. It also contains a single transmembrane domain.

Expression

TEK/Tie2 is predominantly expressed by vascular endothelial cells: It is detectable in the critical process of new vessels formation during early development, and in the adult in response to cyclic hormonal stimulation in the ovary and uterus, as well as in healing skin wounds. High levels of expression of TEK are found in placenta, lung, spleen, and heart tissues. Hematopoietic stem cells, progenitor and mature pericytes, neural progenitor cells, and a subpopulation of monocytes (Tie2-expressing monocytes) also express Tie2/TEK. In addition, its expression might be induced in response to other pathological conditions as described bellow.

Localisation

Cell membrane.

Function

TEK/Tie2 is a tyrosine-kinase transmembrane receptor involved in signaling pathways upon stimuli by angiopoietins (natural ligands). It guides the proper patterning of endothelial cells during blood vessel formation and also plays role in vessel remodeling, cell survival, cell migration, and cell-to-matrix and cell-to-cell adhesion. TEK/Tie2 signaling pathway is also involved in Toll-like receptor 2 and integrin signaling.

Homology

H. sapiens: TEK;
P. troglodytes: TEK;
B. Taurus: TEK;
M. musculus: Tek;
D. rerio: tie2;
R. novergicus: Tek;
G. gallus: TEK.

Mutations

Germinal

Heterozygous TEK substitutions: R849W (10 of 17 families with hereditary mucocutaneous venous malformation, VMCM), Y897S, Y897C, R915H, R918C, V1919L, A925C, K1100N. These mutations result in in vitro ligand-independent hyperphosphorylation.

Somatic

Several somatic mutations have been identified related to non-inherited vascular anomalies:
1) del-Tie2 mutant, consists in an in-frame deletion of 129bp, corresponding to a loss of exon 3 and part of exon 4 (amino acid 122-165 of extracellular Ig-like ligand-binding domain, 43 aa deletion in Ig-like domain);
2) Mutations in exon 17 of TEK/Tie2 in 49,1% (28 of 57 individuals): two somatic TEK mutations (Y897C, R915C) in vascular tumors, and seven somatic TEK mutations in vascular malformations (Y897H, Y897C, L914F, R915C, S917I, R918C, R918H).
In patients with human intramuscular haemangioma, the following Tie2 mutations have been described: G833D, Q837H.

Implicated in

Various cancers

Note
Cancer: acute myeloid leukemia and chronic myelogenous leukemia, and solid tumors, such as malignant gliomas, breast cancer, thyroid cancer, gastric cancer, bladder cancer, endometrial carcinoma.
Present in both the vasculature and cancer cells of several solid tumors.

Disease
Overexpressed in the vasculature of several tumors, as breast cancer, non-small cell lung cancer, hepatocellular carcinoma, prostate cancer, Kaposi's sarcoma, and astrocytoma.
Overexpressed in the cancer cells -outside of the vascular compartment- in acute and chronic myeloid leukemia, and solid tumors, such as malignant astrocytomas, breast cancer, thyroid cancer, gastric cancer, endometrial adenocarcinoma.
Overexpressed in brain tumor stem cells and leukemic blasts.

Prognosis
Correlation of TEK/Tie2 expression and malignancy in gliomas. Tie2 activation results in increased levels of expression of ABC transporter, and eventually chemoresistance of malignant gliomas.
Tie2 regulates migration and invasion of these tumors.
Cellular Tie2 and soluble Tie2 expression might be associated to a higher risk of metastasis in patients with breast and bladder cancer, respectively.

Sporadic and inherited forms of mucocutaneous venous malformations (VMCM) and intramuscular haemangioma

Disease
Venous malformations are vascular masses composed of dilated channels lined by endothelial cells, with a reduced coverage by pericytes, leading to functionally low resistance vessels.
See Mutation section for description of TEK/Tie2 mutations related with these diseases. Some of these mutations affect TEK/Tie2 activity and/or response to ligand.

Prognosis
Not determined.

Systemic sclerosis: microangiopathies

Disease
Systemic sclerosis (SSc) is an autoimmune disease characterized by altered angiogenesis that precede fibrosis of skin and internal organs. The abnormal angiogenesis is one of the major causes of microangiopathies.

Prognosis
Report suggesting that soluble Tie2 in serum samples from patients with systemic sclerosis is related to the development of vascular abnormalities of this disease (nailfold bleeding and pulmonary arterial hypertension).

Cytogenetics
Not determined.

Wide range of diseases with a vascular and/or inflammatory component, such as psoriasis, pulmonary hypertension, rheumatoid arthritis

Disease
Psoriatic lesions are characterized by elongation and dilatation of papillary dermis. Tie2 transgenic mice showed epidermal hyperproliferation, inflammatory cell accumulation, and altered dermal angiogenesis, mimicking the phenotype present in human psoriasis.
Pulmonary hypertension is characterized by high pulmonary arterial pressure. Increased levels of activated TEK/Tie2 and Angiopoietin1 have been reported.
Rheumatoid arthritis is characterized by chronic inflammatory changes in synovial tissue and pathological angiogenesis. Tie2 has been shown to be upregulated in synovial tissue of patients with rheumatoid arthritis and to mediate pathological angiogenesis and invasion within affected synovial tissue.

Prognosis
Not determined.

Cytogenetics
Not determined.

Cerebrovascular disease: stroke

Disease
In stroke, arterial occlusion of one or more arteries in the brain leads to focal or global ischemia and tissue damage and eventual death. Expression of activated

Tie2 and Ang1 lead to enhanced neovascularization, vessel stabilization and improved recovery.

Prognosis

Reports suggest that activation of Tie2-mediated pathway is essential in initiation of survival responses in neural progenitor cells against cerebral ischemia and hypoxia.

Cytogenetics

Not determined.

References

Vikkula M, Boon LM, Carraway KL 3rd, Calvert JT, Diamonti AJ, Goumnerov B, Pasyk KA, Marchuk DA, Warman ML, Cantley LC, Mulliken JB, Olsen BR. Vascular dysmorphogenesis caused by an activating mutation in the receptor tyrosine kinase TIE2. Cell. 1996 Dec 27;87(7):1181-90

Peters KG, Coogan A, Berry D, Marks J, Iglehart JD, Kontos CD, Rao P, Sankar S, Trogan E. Expression of Tie2/Tek in breast tumour vasculature provides a new marker for evaluation of tumour angiogenesis. Br J Cancer. 1998;77(1):51-6

Shewchuk LM, Hassell AM, Ellis B, Holmes WD, Davis R, Horne EL, Kadwell SH, McKee DD, Moore JT. Structure of the Tie2 RTK domain: self-inhibition by the nucleotide binding loop, activation loop, and C-terminal tail. Structure. 2000 Nov 15;8(11):1105-13

Jones N, Iljin K, Dumont DJ, Alitalo K. Tie receptors: new modulators of angiogenic and lymphangiogenic responses. Nat Rev Mol Cell Biol. 2001 Apr;2(4):257-67

Kuroda K, Sapadin A, Shoji T, Fleischmajer R, Lebwohl M. Altered expression of angiopoietins and Tie2 endothelium receptor in psoriasis. J Invest Dermatol. 2001 May;116(5):713-20

Mitsutake N, Namba H, Takahara K, Ishigaki K, Ishigaki J, Ayabe H, Yamashita S. Tie-2 and angiopoietin-1 expression in human thyroid tumors. Thyroid. 2002 Feb;12(2):95-9

Müller A, Lange K, Gaiser T, Hofmann M, Bartels H, Feller AC, Merz H. Expression of angiopoietin-1 and its receptor TEK in hematopoietic cells from patients with myeloid leukemia. Leuk Res. 2002 Feb;26(2):163-8

Shahrara S, Volin MV, Connors MA, Haines GK, Koch AE. Differential expression of the angiogenic Tie receptor family in arthritic and normal synovial tissue. Arthritis Res. 2002;4(3):201-8

Shirakawa K, Shibuya M, Heike Y, Takashima S, Watanabe I, Konishi F, Kasumi F, Goldman CK, Thomas KA, Bett A, Terada M, Wakasugi H. Tumor-infiltrating endothelial cells and endothelial precursor cells in inflammatory breast cancer. Int J Cancer. 2002 May 20;99(3):344-51

DeBusk LM, Chen Y, Nishishita T, Chen J, Thomas JW, Lin PC. Tie2 receptor tyrosine kinase, a major mediator of tumor necrosis factor alpha-induced angiogenesis in rheumatoid arthritis. Arthritis Rheum. 2003 Sep;48(9):2461-71

Du L, Sullivan CC, Chu D, Cho AJ, Kido M, Wolf PL, Yuan JX, Deutsch R, Jamieson SW, Thistlethwaite PA. Signaling molecules in nonfamilial pulmonary hypertension. N Engl J Med. 2003 Feb 6;348(6):500-9

Arai F, Hirao A, Ohmura M, Sato H, Matsuoka S, Takubo K, Ito K, Koh GY, Suda T. Tie2/angiopoietin-1 signaling regulates hematopoietic stem cell quiescence in the bone marrow niche. Cell. 2004 Jul 23;118(2):149-61

Takahara K, Iioka T, Furukawa K, Uchida T, Nakashima M, Tsukazaki T, Shindo H. Autocrine/paracrine role of the angiopoietin-1 and -2/Tie2 system in cell proliferation and chemotaxis of cultured fibroblastic synoviocytes in rheumatoid arthritis. Hum Pathol. 2004 Feb;35(2):150-8

Wang H, Zhang Y, Toratani S, Okamoto T. Transformation of vascular endothelial cells by a point mutation in the Tie2 gene from human intramuscular haemangioma. Oncogene. 2004 Nov 11;23(53):8700-4

Zadeh G, Qian B, Okhowat A, Sabha N, Kontos CD, Guha A. Targeting the Tie2/Tek receptor in astrocytomas. Am J Pathol. 2004 Feb;164(2):467-76

De Palma M, Venneri MA, Galli R, Sergi Sergi L, Politi LS, Sampaolesi M, Naldini L. Tie2 identifies a hematopoietic lineage of proangiogenic monocytes required for tumor vessel formation and a mesenchymal population of pericyte progenitors. Cancer Cell. 2005 Sep;8(3):211-26

Loges S, Heil G, Bruweleit M, Schoder V, Butzal M, Fischer U, Gehling UM, Schuch G, Hossfeld DK, Fiedler W. Analysis of concerted expression of angiogenic growth factors in acute myeloid leukemia: expression of angiopoietin-2 represents an independent prognostic factor for overall survival. J Clin Oncol. 2005 Feb 20;23(6):1109-17

Meunier-Carpentier S, Dales JP, Djemli A, Garcia S, Bonnier P, Andrac-Meyer L, Lavaut MN, Allasia C, Charpin C. Comparison of the prognosis indication of VEGFR-1 and VEGFR-2 and Tie2 receptor expression in breast carcinoma. Int J Oncol. 2005 Apr;26(4):977-84

Wang J, Wu K, Zhang D, Tang H, Xie H, Hong L, Pan Y, Lan M, Hu S, Ning X, Fan D. Expressions and clinical significances of angiopoietin-1, -2 and Tie2 in human gastric cancer. Biochem Biophys Res Commun. 2005 Nov 11;337(1):386-93

Eklund L, Olsen BR. Tie receptors and their angiopoietin ligands are context-dependent regulators of vascular remodeling. Exp Cell Res. 2006 Mar 10;312(5):630-41

Lee OH, Xu J, Fueyo J, Fuller GN, Aldape KD, Alonso MM, Piao Y, Liu TJ, Lang FF, Bekele BN, Gomez-Manzano C. Expression of the receptor tyrosine kinase Tie2 in neoplastic glial cells is associated with integrin beta1-dependent adhesion to the extracellular matrix. Mol Cancer Res. 2006 Dec;4(12):915-26

Macdonald PR, Progias P, Ciani B, Patel S, Mayer U, Steinmetz MO, Kammerer RA. Structure of the extracellular domain of Tie receptor tyrosine kinases and localization of the angiopoietin-binding epitope. J Biol Chem. 2006 Sep 22;281(38):28408-14

Park EH, Lee JM, Pelletier J. The Tie2 5' untranslated region is inhibitory to 5' end-mediated translation initiation. FEBS Lett. 2006 Feb 20;580(5):1309-19

Schliemann C, Bieker R, Padro T, Kessler T, Hintelmann H, Buchner T, Berdel WE, Mesters RM. Expression of angiopoietins and their receptor Tie2 in the bone marrow of patients with acute myeloid leukemia. Haematologica. 2006 Sep;91(9):1203-11

Saito M, Sato Y, Watanabe J, Kuramoto H, Kaba S, Fukuda T. Angiogenic factors in normal endometrium and endometrial adenocarcinoma. Pathol Int. 2007 Mar;57(3):140-7

Cui X, Chen J, Zacharek A, Roberts C, Savant-Bhonsale S, Chopp M. Treatment of stroke with (Z)-1-[N-(2-aminoethyl)-N-(2-ammonioethyl) amino] diazen-1-ium-1, 2-diolate and bone marrow stromal cells upregulates angiopoietin-1/Tie2 and enhances neovascularization. Neuroscience. 2008 Sep 22;156(1):155-64

Martin V, Liu D, Fueyo J, Gomez-Manzano C. Tie2: a journey from normal angiogenesis to cancer and beyond. Histol Histopathol. 2008 Jun;23(6):773-80

Saharinen P, Eklund L, Miettinen J, Wirkkala R, Anisimov A, Winderlich M, Nottebaum A, Vestweber D, Deutsch U, Koh GY, Olsen BR, Alitalo K. Angiopoietins assemble distinct Tie2 signalling complexes in endothelial cell-cell and cell-matrix contacts. Nat Cell Biol. 2008 May;10(5):527-37

Bai Y, Meng Z, Cui M, Zhang X, Chen F, Xiao J, Shen L, Zhang Y. An Ang1-Tie2-PI3K axis in neural progenitor cells initiates survival responses against oxygen and glucose deprivation. Neuroscience. 2009 May 5;160(2):371-81

Chen J, Cui X, Zacharek A, Chopp M. Increasing Ang1/Tie2 expression by simvastatin treatment induces vascular stabilization and neuroblast migration after stroke. J Cell Mol Med. 2009 Jul;13(7):1348-57

Cui X, Chen J, Zacharek A, Roberts C, Yang Y, Chopp M. Nitric oxide donor up-regulation of SDF1/CXCR4 and Ang1/Tie2 promotes neuroblast cell migration after stroke. J Neurosci Res. 2009 Jan;87(1):86-95

Limaye N, Wouters V, Uebelhoer M, Tuominen M, Wirkkala R, Mulliken JB, Eklund L, Boon LM, Vikkula M. Somatic mutations in angiopoietin receptor gene TEK cause solitary and multiple sporadic venous malformations. Nat Genet. 2009 Jan;41(1):118-24

Martin V, Xu J, Pabbisetty SK, Alonso MM, Liu D, Lee OH, Gumin J, Bhat KP, Colman H, Lang FF, Fueyo J, Gomez-Manzano C. Tie2-mediated multidrug resistance in malignant gliomas is associated with upregulation of ABC transporters. Oncogene. 2009 Jun 18;28(24):2358-63

Szarvas T, Jäger T, Droste F, Becker M, Kovalszky I, Romics I, Ergün S, Rübben H. Serum levels of angiogenic factors and their prognostic relevance in bladder cancer. Pathol Oncol Res. 2009 Jun;15(2):193-201

Liu D, Martin V, Fueyo J, Lee OH, Xu J, Cortes-Santiago N, Alonso MM, Aldape K, Colman H, Gomez-Manzano C. Tie2/TEK modulates the interaction of glioma and brain tumor stem cells with endothelial cells and promotes an invasive phenotype. Oncotarget. 2010 Dec;1(8):700-9

Kamal M, El-Khayat W. Do serum angiopoietin-1, angiopoietin-2, and their receptor Tie-2 and 4G/5G variant of PAI-1 gene have a role in the pathogenesis of preeclampsia? J Investig Med. 2011 Oct;59(7):1147-50

Noda S, Asano Y, Aozasa N, Akamata K, Yamada D, Masui Y, Tamaki Z, Kadono T, Sato S. Serum Tie2 levels: clinical association with microangiopathies in patients with systemic sclerosis. J Eur Acad Dermatol Venereol. 2011 Dec;25(12):1476-9

Saber T, Veale DJ, Balogh E, McCormick J, NicAnUltaigh S, Connolly M, Fearon U. Toll-like receptor 2 induced angiogenesis and invasion is mediated through the Tie2 signalling pathway in rheumatoid arthritis. PLoS One. 2011;6(8):e23540

Ye C, Pan L, Huang Y, Ye R, Han A, Li S, Li X, Wang S. Somatic mutations in exon 17 of the TEK gene in vascular tumors and vascular malformations. J Vasc Surg. 2011 Dec;54(6):1760-8

This article should be referenced as such:

Hossain MB, Cortes-Santiago N, Liu D, Martin V, Gomez-Manzano C. TEK (TEK tyrosine kinase, endothelial). Atlas Genet Cytogenet Oncol Haematol. 2012; 16(9):669-673.