

Tie

Key References

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Overview

The Tie family of transmembrane receptor tyrosine kinases is comprised of two highly conserved and related member proteins designated as Tie1 and Tie2. Functional studies of the Tie proteins have demonstrated their essential requirement during normal embryonic development in the establishment of the highly ordered blood vessel network through remodeling of the primary vascular plexus, a process known as angiogenesis. Maintenance of adult vasculature also depends upon functional activation of the Tie receptors and perturbations affecting their exquisite regulation may result in the onset of pathological disorders including cancer, psoriasis, ischemic heart disease, and development of arteriovenous malformations. Although Tie1 and Tie2 are predominantly expressed on endothelial cells, expression has also been detected in other cell types.

Structurally similar, the Tie proteins contain an extracellular ligand binding domain consisting of a number of immunoglobulin-like, epidermal growth factor-like, and fibronectin type III subdomains followed by a transmembrane region, an intracellular catalytic tyrosine kinase domain, and a carboxyl terminal tail region. While no ligand has been identified for Tie1, mutational studies have facilitated the elucidation of some of the functions of this orphan receptor. Loss of Tie1 function in a murine model results in embryonic lethality between E13.5-birth due to widespread hemorrhaging and edema caused by loss of vascular integrity and endothelial cell death. Chimeric analyses of Tie1/Tie2 deficient cells have also implicated their potential function in the regulation of adult hematopoiesis. While chimeric receptor studies have demonstrated Tie1's ability to stimulate Phosphatidylinositol 3OH Kinase

(PI3K) activity and enhance endothelial cell survival, the absence of an activating ligand for Tie1 however, has hindered more extensive studies of its intracellular signaling capabilities and enzymatic regulation.

In sharp contrast to its familial counterpart, functional analysis of Tie2 has been greatly furthered by the discovery and isolation of the angiopoietins, a family of four soluble ligands (Angiopoietin 1-4) specific for Tie2. While Ang1, Ang3, and Ang4 behave as agonists of Tie2 activity, Ang2 appears to operate predominantly as a competitive antagonist; however, additional studies have indicated that Ang2 may also serve as an activator of Tie2 within certain cell contexts. Ang3 and Ang4 are thought to represent inter-species orthologs, with Ang3 as the murine counterpart of human Ang4. Similar to the effects observed in Tie2 deficient mice, loss of Ang1 causes early embryonic lethality (day E9.5-E12.5) due to impaired development of the endocardium and insufficient vascular expansion. Ang1-dependent activation stimulates the recruitment of supporting pericyte and smooth muscle cells to nascent vessels and enhances endothelial cell migration and survival, thereby functioning in the stabilization of newly formed blood vessels. Ligand binding induces receptor dimerization and autophosphorylation resulting in the subsequent recruitment of intracellular downstream signaling binding partners including Dok-R and the p85 subunit of PI3K. While Dok-R mediates endothelial cell migration through recruitment and activation of Nck and the serine/threonine kinase Pak and consequent reorganization of the actin cytoskeleton, stimulation of PI3K activity enhances cell survival via activation of the serine/threonine kinase Protein Kinase B (PKB, also called Akt) and inhibition

of apoptosis. Additional Tie2 binding partners include the docking protein Grb2 and the protein phosphatase Shp2 although their functional relevance remains to be characterized.

Although the therapeutic value of modulation of the Tie receptor system has not been extensively tested, it remains an enticing potential target. Targeted activation of the Tie receptors within ischemic or hypoxic tissues could result in increased local neovascularization and the consequent recovery of the diseased tissue. Alternately, repression of Tie-dependent angiogenesis within cancer cells may impair metastasis and delay tumor progression, potentially leading to complete tumor regression.

Tie

FAMILY MEMBERS	Tie 1	Tie 2
OTHER NAMES	JTK14, TIE, tyrosine kinase receptor 1, tyrosine kinase with immunoglobulin and epidermal growth factor homology domain	Endothelial-specific receptor tyrosine kinase, Hyk, endothelial (venus malfunctions, multiple cutaneous and mucosal), VMCM, VMCM1, CDC202, TEK
MOLECULAR WEIGHT/ STRUCTURAL DATA	125 kDa, 1138 aa	126 kDa, 1124 aa
ISOFORMS	Not known	Not known
SPECIES	Bovine, zebrafish, human, mouse	Bovine, zebrafish, human, mouse, rat
DOMAIN ORGANIZATION	3 EGF-like domains, 3 fibronectin type-III domains, 2 Ig-like C2-type domains	3 EGF-like domains, 3 fibronectin type-III domains, 2 Ig-like C2-type domains
PHOSPHORYLATION SITES	Tyr ¹⁰⁰⁷	Tyr ⁹⁹² , Tyr ¹¹⁰⁶
TISSUE DISTRIBUTION	Endothelial cells, hematopoietic cells (stem, myeloid, platelets)	Endothelial cells, hematopoietic cells (stem, neutrophils), endothelial progenitor cells, keratinocytes
SUBCELLULAR LOCALIZATION	Plasma membrane	Plasma membrane
BINDING PARTNERS/ ASSOCIATED PROTEINS	Tie2, p85 subunit of PI3K	DOK2, DOK4, Angptl 1, Cbfb, GRB2, GRB7, GRB14, PTPN11, SOCS1, Ang2, Ang1, Ang3
UPSTREAM ACTIVATORS	TFN- α , PMA, VEGF, PKC, angiopoietin	Angiopoietin, ANG1, ANG2
DOWNSTREAM ACTIVATION	Tie1	p85 subunit of PI3K
ACTIVATORS	Not known	Not known
INHIBITORS	Not known	Not known
SELECTIVE ACTIVATORS	Not known	Not known
PHYSIOLOGICAL FUNCTION	Developmental vascular remodeling; maintenance of adult vasculature; postnatal hematopoiesis; regulation of arteriovenous cell polarity	Developmental vascular remodeling; maintenance of adult vasculature; postnatal hematopoiesis; regulation of arteriovenous boundaries; regulation of vascular permeability
DISEASE RELEVANCE	Cancer, arteriovenous malformations, atherosclerosis	Cancer, arteriovenous malformations, atherosclerosis, diabetic retinopathy, cardiac hypertension, psoriasis, goiter

FOOTNOTES