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Gene Section
Review

TRIB1 (tribbles pseudokinase 1)

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Abstract

Review on TRIB1, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords
TRIB1

Identity

Other names: C8FW, GIG-2, GIG2, SKIP1

HGNC (Hugo): TRIB1

Location
8q24.13; Transcript (including UTRs) chr8:126,442,563-126,450,644 Coding region: chr8:126,443,145-126,448,713.

Note
The tribbles family of genes encode a group of highly conserved pseudokinase proteins, which are thought to act as adaptors in several signalling pathways that are intimately involved in the regulation of a number of key cellular processes, including MAPK, and PI3K pathways. Tribbles have also been shown to interact with ubiquitin ligases, thereby promoting degradation of target proteins. Tribbles have been implicated in a number of diseases including leukaemia, metabolic syndromes and cardiovascular disease.
Tribbles proteins were first discovered in Drosophila as a negative regulator of string/cdc25, where when over-expressed directly inhibited mitosis (Grosshans and Wieschaus 2000). Simultaneously, TRIBs were found to promote the degradation of string via the proteasome pathway and showed that overexpression of tribbles in imaginal disc cells blocked the cell cycle at G2 resulting in abnormal wing morphology (Mata, et al 2000). Since then three highly conserved mammalian homologues have been indentified; Trib1, Trib2 and Trib3.

DNA/RNA

Transcription

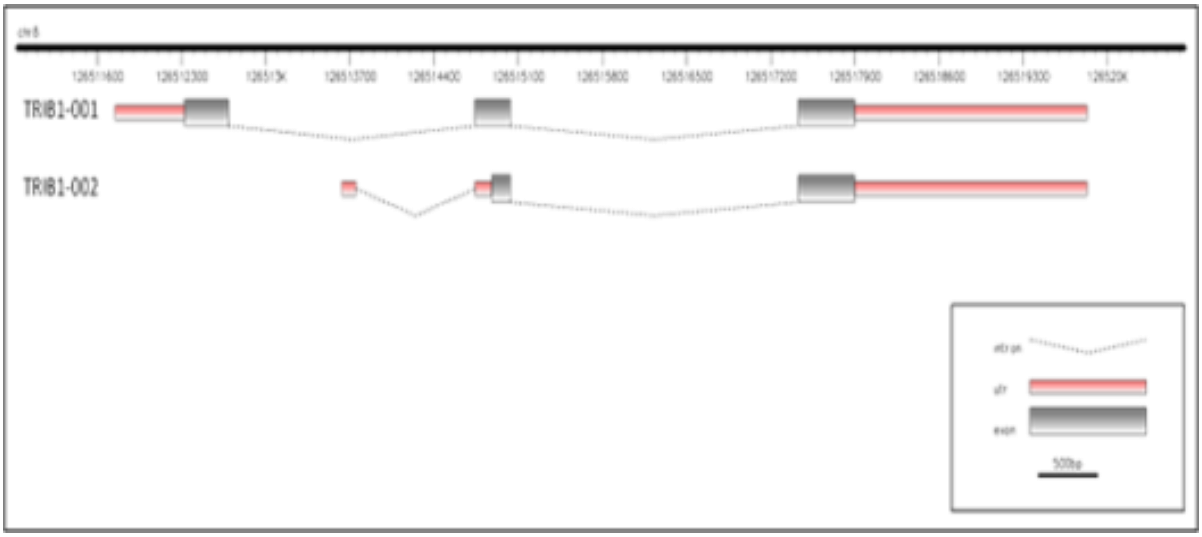
There are two protein coding transcripts of TRIB1; TRIB1-001 and TRIB1-002.
TRIB1-001 (Isoform 1); Transcript size: 3,635bp; Exon count: 3.
TRIB1-002 (Isoform 2); Transcript size: 1,332 bp; Exon count: 2

Protein

Note
TRIB1-001: 372 amino acids; TRIB1-002: 206 amino acids

Description

TRIB1 contain a N terminal (NT) domain of 60-80 residues and a C-terminal domain of 35-40 residues and a characteristic single central Ser/Thr kinase-like (pseudokinase) domain. TRIB1 contains features consistent with its emerging role as a protein adaptor in signalling pathways.
N-Terminal Domain The NT fragment of TRIB1 is proline and serine rich, mostly in the sequence adjacent to the kinase-like domain. The abundance of these amino acids are a characteristic of PEST proteins that are involved in controlling the half life of proteins by altering their susceptibility to degradation.



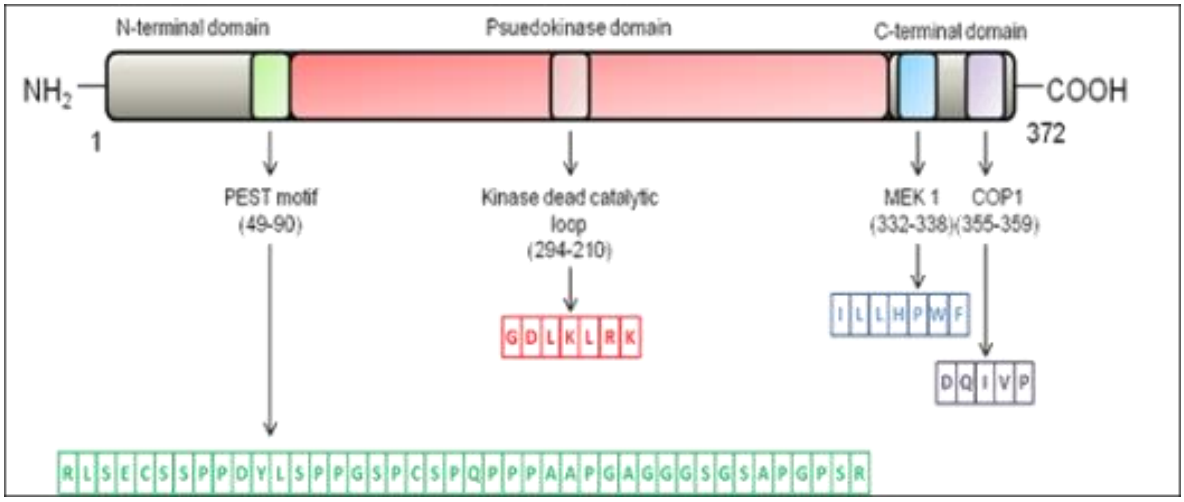
There are two validated transcripts of TRIB1 (NM_025195 and NM_001282985) coding for isoforms 1 and 2 respectively. Isoform 2 has a shorter 5'UTR (untranslated region) and 5' coding region compared to isoform 1 and initiates translation further downstream. UTRs and exons are represented by the red and grey boxes respectively. Image drawn by FancyGene (Rambaldi and Ciccarelli 2009).

Other functions of these types of proteins include the anchoring of SH3 or WW domains of other proteins or acting as a substrate for proline dependent phosphorylation. TRIB1 contains possible phosphorylation sites for proline-dependent kinases (Hegedus, et al 2007).

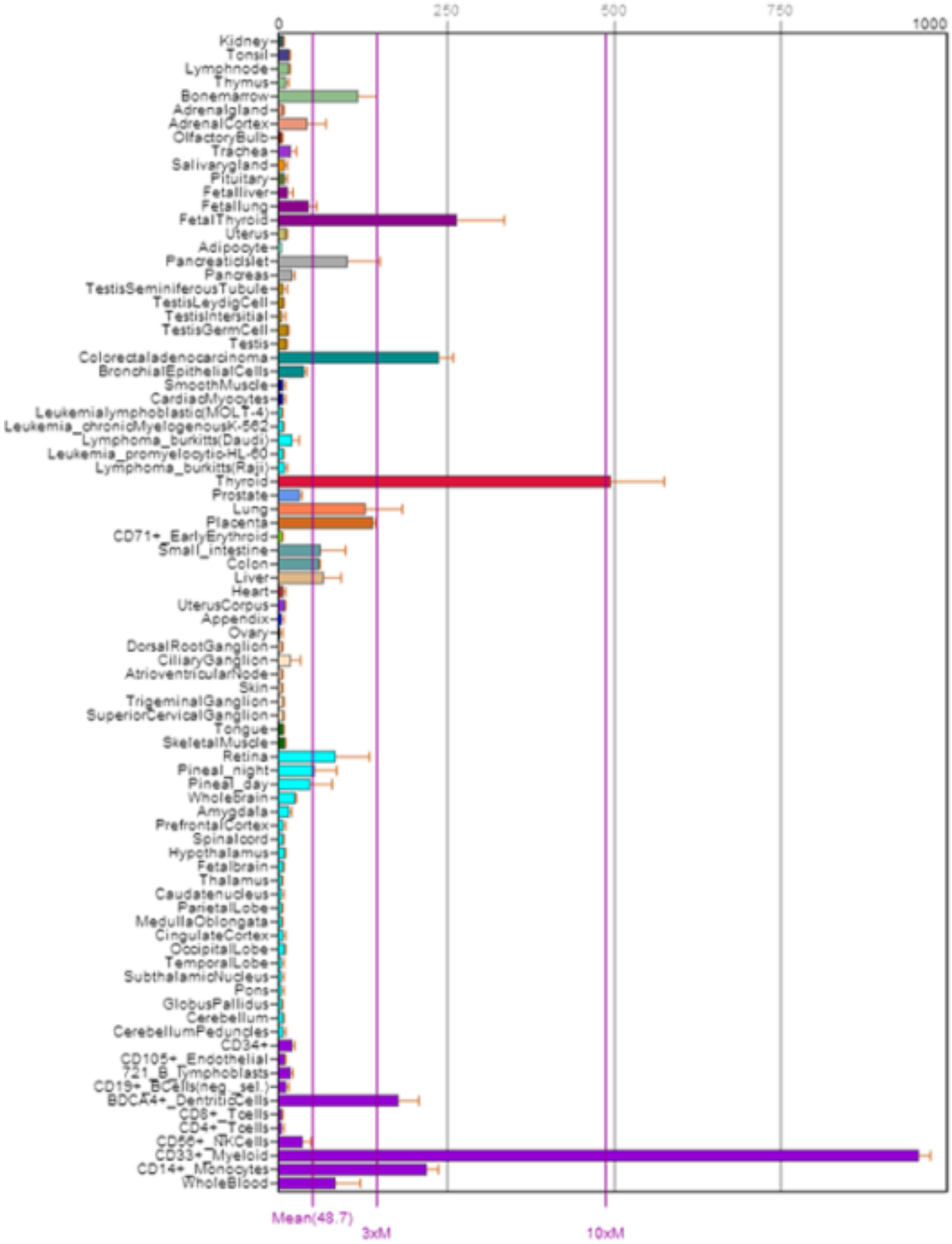
TRIB1 also contains two evolutionary conserved motifs. The first consists of a putative nuclear localisation signal, [K/R]2X2[D/E]X[D/E].

The second motif contains a G-S-P consensus pattern found close to the kinase-like domain. The G-S-P motif is present in human SNIP1 (Smad nuclear interacting protein) which functionally associates with BGR1, which interacts with the Drosophila homologue of Slbo, C/EBP transcription factors (Beausoleil, et al 2004, Kadam, et al 2000). C/EBP transcription factors have been shown to functionally and physically interact with TRIB1 promoting their degradation (Yoshida, et al 2013).

Kinase-like domain TRIB1 contains a Ser/Thr kinase-like domain that is composed of some of the motifs present in catalytically active kinases such as a Lysine crucial for ATP binding whilst others are missing. Despite this evidence would suggest TRIB1 no to possess kinase activity.



Protein structure of Tribbles 1: TRIB1 has a N terminal, pseudokinase and C terminal domains. It contains four protein motifs; a putative PEST sequence, a kinase dead catalytic loop, a MEK1 binding and COP1 binding motif. The characteristic amino acid sequence for each motif is shown along with location.



The tissue specific expression of human TRIB1 mRNA is shown. Data and figure taken from BioGPS. Additional microarray expression data from the Human Gene Expression Atlas from the Genomics Institute of the Novartis Research Foundation (GNF) can be found on the UCSC browser (http://genome.ucsc.edu/) (Su, et al 2004, Wu, et al 2009).

Protein	Mode of Interaction	Biological Significance	Reference
MEK-1	Interaction by C-terminal ILXHPW[F/L] motif	Enhancement of ERK phosphorylation and myeloid leukaemia induction	Kiss-Toth, *et al* (2004) Yokoyama, *et al* (2010)
MKK4	Interaction by the C-terminus	Suppression of vascular smooth muscle migration	Sung, *et al* (2007)
COP1	Interaction by the C-terminal [D/E]QXVP[D/E] motif	Degradation of target proteins	Keeshan, *et al* (2006) Qi, *et al* (2006)
C/EBPα	Proteasome-mediated degradation	Myeloid leukaemia induction	Keeshan, *et al* (2006) Yokoyama, *et al* (2010)
C/EBPβ	Proteasome-mediated degradation	Inhibition of adipocyte differentiation, modification of toll-like receptor signalling	Naiki, *et al* (2007)

However this domain is highly conserved during evolution suggesting it is important for the role of TRIB1(Hegedus, et al 2007).

C-Terminal Domain The CT domain is around 35-45 amino acids long and is rich in charged amino acids important for protein interactions. Two important motifs have been identified in the CT domain; a hexapeptide motif [D/E]QXVP[D/E] as a COP1 (E3 ubiqutin ligase) binding site, essential for proteasome mediated degradation of C/EBPα family members and a MEK 1 binding site (ILLHPWF) (Hegedus, et al 2007).

Post translational modifications Several post translational modifications of TRIB1 have been reported and validated by mass spectrometry and listed in the PhosphoSitePlus database (Hornbeck, et al 2012).

Expression

TRIB1 expression is ubiquitious with highest expression in the thyroid and myeloid cells (Figure). TRIB1 is thought to expressed in a cell-type specific manner (Sung, et al 2006).

Localisation

Numerous over-expression experiments have shown TRIB1 to be located in the nucleus. It contains a putative nuclear localisation signal (Yokoyama, et al 2010).

Function

TRIB1 has been shown to interact with a number of proteins as detailed herein (Table1):

MEK-1 and MKK4 Co-immunoprecipitation experiments have shown specific interactions with MEK1 (an ERK activator MAPKK) and MKK4 (a JNK activator MAPKK). Interactions with Tribbles control the extent and specificity of MAPK activation and are dependent on levels of TRIB expression (Kiss-Toth, et al 2004, Sung, et al 2007). MEK1 phosphorylates ERK which in turn promotes cell proliferation and suppression of apoptosis. The interaction between TRIB1 (via ILLHPWF motif) and MEK1
enhances ERK phosphorylation as mutants lacking the motif were unable to do so (Yokoyama, et al 2010) .

TRIB1 also interacts with MKK4, a JNK activator and implicated in the migration and proliferation of smooth muscle and involved in the pathogenesis of atherosclerosis. The nuclear localisation of TRIB1-MKK4 complex is dependent on the NT domain of TRIB1, however the central kinase-like domain of TRIB1 is sufficient for its interaction with MKK4 but the interaction is no longer preferentially nuclear (Sung, et al 2007).

COP1 AND C/EBPalpha TRIB1 contains a COP1 binding site at the carboxy terminus. COP1 is an E3 ubiquitin ligase that promotes the transfer of ubiquitin to target substrates for degradation via the proteasome. One of the prinicipal targets of COP1 are the family of transcription proteins CCAT/enhancer binding proteins (C/EBPs). It is thought TRIB1 acts to negatively regulate C/EBP proteins by acting as adaptors to recruit COP1 to C/EBP family members thereby promoting ubiquitination and degradation. Studies have shown that COP1 requires TRIB1 for its action of C/EBPα (Yoshida, et al 2013).

Homology

TRIB1 homologues have been indentified in different species including mouse, frog and zebrafish. Table 2 illustrates some of the TRIB1 homologues.

Species	Symbol	Gene ID (NCBI)	Protein	DNA
***H.sapiens* vs.**	**TRIB1**	**10221**		
P.Troglodytes (chimpanzee)	TRIB1	464388	99.5	99.3
M. Mulatta (Rhesus monkey)	TRIB1	693459	98.9	97.2
C.Lupus (grey wolf)	TRIB1	482039	96.8	93.6
B.Taurus (cattle)	TRIB1	521857	96.8	92.1
M.Musculus (house mouse)	Trib1	211770	93.8	88.4
R.Norvegicus (brown rat)	Trib1	78969	93.5	88.8
G.Gallus (chicken)	LOC428386	776883	91.3	80.8

Table 2: protein and DNA identity of human TRIB1 vs other species. Data taken from Homologene and NCBI.

Mutations

Note

A somatic point mutation of TRIB1 has been reported in Down syndrome (DS)- related acute megakaryocytic leukaemia (AMKL) (Yokoyama, et al 2012). A G:T point mutation was found in the pseudokinase domain resulting in an amino acid change from arginine to leucine (R107L). When the mutation was expressed in mouse bone marrow cells and transferred into lethally irradiated recipient mice there was a more rapid development of AML and enhancement of ERK phosporylation suggesting a gain of function mutation. Yokoyama, et al (2012) suggests that the mutation of TRIB1 is an early event in leukaemogenesis.

A wide range of allelic variants of TRIB1 have been reported. There are several genetic and protein variations of TRIB1 listed on Ensembl.

Table (3) shows the types of genetic variation of TRIB1. Data taken from: http://Feb2014.archive.ensembl.org/Homo_sapiens/Gene/Variation_Gene/Table?db=core;g=ENSG00000173334;r=8:126442563-126450647

Protein variants of TRIB1: Table 4 shows the protein variants of TRIB1. Each variant is listed in order according to residue number. The table also lists SIFT and Poly-Phen scores for the variations. SIFT predicts whether an amino acid substitution is likely to affect protein function based on the sequence homology and the physico-chemical similarity between the alternate amino acids. Each variant is accompanied with a score and predictive consequence that is based on the probability that the amino acid change is tolerable. A score closer to 0 is more likely to be deleterious. A score of <0.05 are deleterious and all others are 'tolerated'. PolyPhen predicts the effect of an amino acid substitution on the structure and function of a protein using sequence homology. A PolyPhen score represent the probability that a substitution is damaging, scores nearer to 1 are more confidently to be predicted to be deleterious (opposite to SIFT score). Each score is colour coded according to damage (SIFT; Red= deleterious, Green= tolerated. PolyPhen; Red= probably damaging, Orange= possibly damaging, Green= benign) (Adzhubei, et al 2010, Gonzalez-Perez and Lopez-Bigas 2011, Kumar, et al 2009). Data taken from: http://Feb2014.archive.ensembl.org/Homo_sapiens/Transcript/ProtVariations?db=core;g=ENSG00000173334;r=8:126442563-126450647;t=ENST00000311922

Somatic

See online: Table 4: Protein variants of TRIB1.

Implicated in

Smooth muscle cells

TRIB1 is selectively over-expressed in chronically inflamed human atherosclerotic arteries and regulates vascular smooth muscle cell (VSMC) chemotaxis and proliferation, a characteristic feature of atherosclerosis via the JNK pathway (Sung, et al 2007).

	Number of variant consequences	Type	Description
	6	Stop gained	A sequence variant whereby atleast one base of a codon is changed resulting in a premature stop codon , leading to a shortened transcript
	5	Frameshift variant	A sequence variant which causes a disruption of the translational reading frame, because the number of nucleotides inserted or deleted is not a multiple of three
	1	Inframe deletion	An inframe non synonymous variant that deletes bases from the coding sequence
	70	Missense variant	A sequence variant, that changes one or more bases, resulting in a different amino acid sequence but the length is preserved
	3	Spice region variant	A sequence variant in which a change has occurred within the region of the splice site, either within 1-3 bases of the exon or 3-8 of the intron
	37	Synonymous variant	A sequence variant there there is no resulting change to the encoded amino acid
	18	5 prime UTR variant	A UTR variant in the 5' UTR
	33	3 prime UTR variant	A UTR variant in the 3' UTR
	118	Intron variant	A transcript variant occurring within an intron
	116	Upstream gene variant	A sequence variant located 5' of a gene
	107	Downstream gene variant	A sequence variant located 3' of a gene
TOTAL	511		

Table 3: Genetic variations of TRIB1

Macrophages

Trib1 is expressed in plaque resident macrophages in murine experimental atherosclerosis. The expression of Trib1 could be upregulated by IL-1, a major contributor to plaque development as the percentage of Trib1 expressing macrophages significantly decreases in ApoE -/- IL1R-/- double knockout mice compared to ApoE-/- controls. Overexpression of Trib1 in macrophages in vitro also leads to a significant attenuation (~70%) of IL-6 production and suppressed IL-12 expression induced with a pro-inflammatory stimulus (Sung, et al 2012).

It has also been shown that TRIB1 is involved in macrophage migration through interactions with C/EBPβ and TNF-a. Knockdown of TRIB1 in RAW246.7 cells resulted in an increase in TNF-a production and C/EBPβ expression suggesting TRIB1 may modulate TNF-a through C/EBPβ (Liu, et al 2013).

Trib1 has been shown to also be involved with adipose tissue maintenance and suppression of metabolic disorders by controlling the differentiation of tissue M2-like macrophages. Trib1 deficiency results in a significant reduction of M2-like macrophages. Mice lacking Trib1 in haematopoietic cells show a reduced adipocyte tissue mass and have evidence of increased lipolysis even on a normal diet. Supplementation of M2-like macrophages causes rescue suggesting the lack of these M2-like macrophages are responsible for lipolysis.

When mice are fed a high fat diet, mice lacking Trib1 in haematopoietic cells develop hypertriglyceridaemia and insulin resistance and a pro-inflammatory cytokine induction (Satoh, et al 2013).

Cancer

TRIB1 has been associated with the development of cancer and is considered as a leukaemia disease gene. It was identified as a collaborator of *Hoxa9* and *Meis1* in myeloid leukaemogenesis (Jin, *et al* 2007). Cooperative genes for *Hoxa9/Meis1* were identified as common targets for retroviral integration, where TRIB1 was identified as the most frequent common site for integration in AML (Nakamura 2005). Table 5 shows the common integration sites and candidate cooperative genes in TRIB1-induced AML (Yokoyama and Nakamura 2011). TRIB1 alone is a transforming gene for myeloid cells and also significantly accelerates the development of *Hoxa9/Meis1* AML.

Table 5: Common integration sites and candidate cooperative genes in TRIB1-induced AML.

Species	Symbol	Gene ID (NCBI)	Protein	DNA
***H.sapiens* vs.**	**TRIB1**	**10221**		
P.Troglodytes (chimpanzee)	TRIB1	464388	99.5	99.3
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G.Gallus (chicken)	LOC428386	776883	91.3	80.8

Oncogenesis

Phosphorylation of ERK is enhanced in TRIB1 transfected HeLa and Baf3 cells and leukaemia cells derived from TRIB1-induced AML upon cytokine stimulation (Jin, *et al* 2007).

MEK1 and enhancement of MEK/ERK phosporylation is required for reactivity. Mutant lacking MEK1 binding site is unable to enhance phosphorylation of ERK or extend self renewal in bone marrow cells or induce AML/accelerate *Hoxa9/Meis1* induced AML (Yokoyama, *et al* 2010).

TRB1 has been implicated in human AML. *TRIB1* is found on chromosome 8q24, 1.5Mb away from *c-MYC*, the target of AML amplification. TRIB1 is over-expressed even in some cases of AML when *c-MYC* amplification is not detected (Roethlisberger, *et al* 2007, Storlazzi, *et al* 2006)

Cardiovascular Disease and Atherosclerosis

Emerging evidence from several genome-wide association studies (GWAS) has implicated TRIB1 in the risk of cardiovascular disease and events specifically due to the levels of circulating lipids (Kathiresan, et al 2008, Willer, et al 2008).

Two SNPs (rs2954029 and rs17321515) near the TRIB1 gene have been implicated with triglyceride, LDL and HDL levels. A minor G allele at rs17321515 was associated with lower triglyceride and LDL cholesterol and higher HDL cholesterol levels. A TT -> TA -> AA genotypes at rs2954029 were associated with step wise increases in the levels of triglyceride, remnant cholesterol and apo-lipoprotein B, the primary apolipoproteins present on LDLs. Likewise HDL cholesterol levels decreased step-wise through the genotypes. Additionally the genotypes were found to be significantly associated with increased risk of ischemic heart disease (IHD) and increased risk of MI.

Further bivariate analysis showed TRIB1 expression to be significantly associated with triglyceride/ elevated blood pressure and triglyceride/HDL-cholesterol suggesting TRIB1 may be involved in a specific feature of lipid homeostasis (Kraja, *et al* 2011).
NOTE These genetic studies were further validated in *in vivo* models. Specific hepatic over-expression of *Trib1* using an adenovirus vector reduced lipid plasma levels in a dose-dependent manner due to reduced VLDL production. Equally the opposite was seen in *Trib1*- knockout mice due to increased VLDL production. Interestingly when hepatic expression was reconstituted in knockout mice, VLDL-triglyceride production decreased to levels found in control mice (Burkhardt, *et al* 2010). The precise mechanisms of Trib1 involvement in lipid metabolism however are unknown.
NOTE Burkhardt, et al (2010) further investigated by examining the mRNA levels of genes associated with lipid metabolism in the livers of *Trib1* over-expressing and *Trib1*- deficient mice. A significant decrease was found for genes involved in fatty acid oxidation such as *Cpt1a* (carnitine palmitoyltransferase 1A), *Cpt2*, and *Acox1* (acyl-Coenzyme A oxidase 1) in *Trib1* $^{-/-}$ mice. A significant up-regulation of key lipogeneic genes was also found such as *Acc1* (acetyl-Coenzyme A carboxylase), fatty acid synthesis (*Fasn*) and stearoyl-Coenzyme A desaturase 1(*Scd1*). Significant downregulation of these genes were found in *Trib1*-over expressing mice. These genes have been noted to have effects on VLDL secretion and plasma triglyceride and cholesterol levels. TRIB1 may also have a further role in lipogenesis. *TRIB1* over-expression resulted in a significant decrease in 35S-methionine labelled apoB secretion in HepG2 cells (human liver carcinoma cell line). The authors speculate that *TRIB1*-mediated regulation of hepatic lipid availability might alter the secretion of apoB particles via a mechanism involving ER-associated degradation (ERAD) as previous data has shown a reduced availability or synthesis of lipid for apoB lipidation leads to co-translational targeting of apoB for ERAD (Ginsberg, *et al* 2009).

Type 2 Diabetes

Trib1 has been hypothesised to have a regulatory role in inflammation in adipoctyes that may contribute towards obesity related type 2 diabetes. Trib1 is specifically up-regulated during acute and chronic inflammation in white adipose tissue in mice. Trib1 knockout mice show it to be a key regulator of inflammatory cytokines such as TNF-a and are protected from high fat diet induced obesity (Ostertag, *et al* 2010). It is proposed that Trib1 is pro-inflammatory in the adipose by acting as a co-activator for NF-kB inducing the expression of proinflammatory cytokines.

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