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Gene Section
Short Communication

ZAP70 (zeta-chain (TCR) associated protein kinase 70kDa)

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Abstract

Review on ZAP70, with data on DNA, on the protein encoded, and where the gene is implicated.

Identity

Other names: SRK, STD, STCD, TZK, FLJ17670, FLJ17679

HGNC (Hugo): ZAP70

Location : 2q11.2

DNA/RNA

Description

The ZAP70 gene encodes an enzyme belonging to the protein tyrosine kinase (PTK) family, and it plays a role in T-cell development and lymphocyte activation. The cDNA clone encoding human ZAP70 was identified for the first time by Chan et al. in 1992 (Chan 1992), and mouse cDNA for both ZAP70 and Syk was cloned two years later (Ku 1994). Mutations in this gene cause selective T-cell defect, a severe combined immunodeficiency (SCID) disease characterized by a selective absence of CD8-positive T-cells (review in Wang 2010).

Transcription

The transcript encodes 619 amino acids with a mass of 69,872 Da. Three isoforms have been described (http://www.uniprot.org/uniprot/P43403#structure): Isoform 1 (full-length); Isoform 2 (1-307 is missing); Isoform 3 (1-126 is missing; 127-134 VRQTWKLE->MRLGPRWK).

Protein

Description

ZAP70 is composed of two SH2 domains and a carboxy-terminal kinase domain (Fig. 1). The crystal structure of the tandem SH2 domains of the human PTK ZAP70 in complex with a peptide derived from the zeta-subunit of the T-cell receptor (TCR) was revealed by Hatada et al (Hatada 1995). A coiled coil of alpha-helices connects the two SH2 domains, producing an interface that constitutes one of the two critical phosphotyrosine binding sites, providing the molecular basis for highly selective association of ZAP70 with the T-cell receptor.

The crystal structure of autoinhibited ZAP70 revealed a new mechanism for maintaining an inactive kinase domain conformation (Deindl 2007), which also have been shown in cell-based experiments (Brdicka 2005; Deindl 2009). The two tandem SH2 domains that are separated by a linker region, termed interdomain A. Upon activation, conformational changes in ZAP70 promote disassembly of the interface mediating the autoinhibited conformation, and exposure of tyrosines Y292, Y315 and Y319 in interdomain B, leading to their phosphorylation that further destabilizes the interface (Wang 2010).

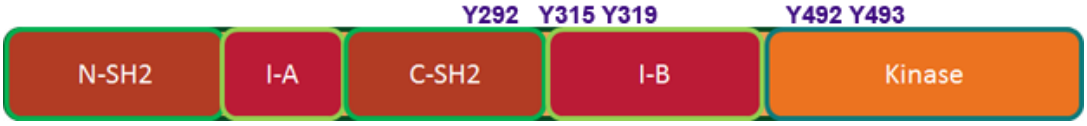

Figure 1. Schematic structure of inactive ZAP70 (adopted from Wang et al 2010). The ZAP70 domains indicated are the amino-terminal SH2 domain (N-SH2), interdomain A (I-A), carboxy-terminal SH2 domain (C-SH2), interdomain B (I-B) and the kinase domain.

Expression

ZAP70 protein is expressed in all major thymocyte populations, with the level of expression being comparable to that found in both CD4+ and CD8+ peripheral T cells (Chan 1991;Irving 1993). Stimulation of the TCR results in tyrosine phosphorylation of a number of cellular substrates. One of these is the TCR zeta chain, which can mediate the transduction of extracellular stimuli into cellular effector functions. When ZAP70 was discovered, it represented a novel PTK and was found to be expressed in T cells and natural killer (NK) cells. The tyrosine phosphorylation and association of ZAP70 with TCR zeta was shown to require the presence of src family PTKs and provide a potential mechanism by which the src family PTKs and ZAP70 may interact to mediate TCR signal transduction (Chan 1991;Irving 1993).

The first indication that ZAP70 may be expressed in the B cell lineage came from studies of B-cell chronic lymphocytic leukemia (CLL) (Rosenwald 2001). ZAP70 was thereafter also reported to be expressed throughout B cell development at different maturational stages and that it plays a role in the transition of pro-B to pre-B cells in the bone marrow, a checkpoint controlled by signals from the pre-B cell receptor (pre-BCR), which monitors for successful rearrangement of immunoglobulin heavy chain genes (Schweighoffer 2003; Nolz 2005; Crespo 2006; Scielzo 2006).

Localisation

In the cytoplasmic compartment of the T-cell, once recruited to tyrosines in the immunoreceptor tyrosine-based activation motif (ITAM) of the TCR- subunit, ZAP70 is activated by phosphorylation, at Tyr-493 in its activation loop, by Lck (Chan 1995; Wange 1995). Upon phosphorylation, these bound ZAP70 molecules autophosphorylate to create docking sites for SH2-domain-containing signalling proteins (Neumeister 1995; Katzav 1994; Couture 1994; Duplay 1994). Docking of ZAP70 at the plasma membrane is required for its activation (reviewed in Fischer 2010).

Function

Indeed, PTKs play an integral role in T cell activation. TCR signal transduction and the events leading to activation of downstream signaling pathways involve many molecules, including the PTKs Src, Syk, Csk and Tec families, as well as adaptor proteins and effector enzymes in tyrosine phosphorylation cascades (review in Mustelin, 2003). Both SH2-domains of ZAP70 are crucial for high avidity binding and for function in signal transduction (Bu 1995; review by Au-Yeung 2009 and Wang 2010). ZAP70 is phosphorylated on tyrosine residues upon TCR stimulation, and functions in the initial step of TCR-mediated signal transduction in combination with the clustering of coreceptor (CD4 or CD8)-associated LCK with T cell receptors allows Lck to phosphorylate tyrosine residues in ITAMs in the intracellular tails of zeta chains of the TCR-complex (Yan 2013). Doubly phosphorylated ITAMs in the stimulated TCR complex recruit ZAP-70 to the plasma membrane. Activated ZAP70 subsequently phosphorylates at least two critically important adaptor proteins, linker for the activation of T cells (LAT) and SH2-domain-containing leukocyte phosphoprotein of 76 kDa (SLP-76) (Bubeck Wardenburg 1996; Zhang 1998; Au-Yeung 2009). Interdomain B in the ZAP70 molecule, between the C-terminal SH2-domain and the kinase domain, is also a critical region because of the three tyrosine residues Y292, Y315 and Y319 that are phosphorylated by Lck upon TCR-triggering (Fischer 2010). The tyrosine Y292 binds the ubiquitin ligase c-Cbl and control both zeta (of the TCR-CD3-zeta complex) ubiquitination and TCR downmodulation, whereas Y315 interacts with the CT10 regulator of kinase II (CrkII) adapter protein (Lupher 1997; Gelkop 1999; Fischer 2010). The tyrosine Y319 is also a binding site for PLC-gamma , resulting in a positive ZAP70 kinase-mediated regulation through PLC-gamma phosphorylation and Ca^{2+} mobilization (Di Bartolo 1999; Williams 1999). The kinase domain itself also contains two tyrosine residues that are phosphorylated. Phosphorylation of Y493 by Src-family PTKs upregulate ZAP70 activity, whereas phosphorylation of Y492 seems to do the opposite, by negatively regulate ZAP70 kinase activity (Chan 1995; Wange 1995). Moreover, the low molecular weight protein-tyrosine phosphatase (LMPTP) specifically dephosphorylates the negative regulatory Tyr-292 of ZAP-70, thereby counteracting inactivation of ZAP70 (Bottini 2002). The proteins phosphorylated by ZAP70 are not that well investigated. VHR , a

Vaccinia virus VH-1 related dual-specific protein phosphatase that inactivates the mitogen-activated kinases Erk1 and Jnk, is phosphorylated at Y138 by ZAP70 (Alonso 2002).
The role of ZAP70 in B cells has been investigated, but is poorly understood possibly due to the functional redundancy between Syk and ZAP70 (Fallah-Arani 2008). Studies in CLL reveal that the ability of ZAP70 to enhance BCR signalling was independent of its kinase activity as both WT ZAP70 and a catalytically inactive ZAP70 mutant induced similar increases in intracellular free Ca2+ concentration upon BCR triggering (Chen 2008).

Homology

Together with Syk, ZAP70 defines the Syk family of PTKs, with structural homology composed of non-myristylated cytoplasmic peptides of two N-terminal Src-homology 2 (SH2) domains and a C-terminal catalytic domain (Taniguchi 1991; Chan 1992). Although Syk protein is also present in all thymocyte subsets, expression of Syk protein is down-regulated three- to fourfold in peripheral T cells. In contrast to ZAP70, expression of Syk is 12- to 15-fold higher in peripheral B cells when compared with peripheral T cells (Chan 1994a). Both ZAP-70 and Syk are dependent upon a Src-family protein tyrosine kinase for association with the phosphorylated zeta-chain. Thus, the differential expression of these kinases suggests the possibility of different roles for ZAP70 and Syk in TCR signaling and thymic development (Palacios 2007). Another study showed functional homology in antigen receptor signaling by demonstrating that expression of ZAP70 in Syk- B cells reconstitutes BCR function (Kong 1995). Reconstitution required the presence of functional Src homology 2 (SH2) and catalytic domains of ZAP70. In addition, they demonstrated that both ZAP70 and Syk can bind directly to the phosphorylated Ig alpha and Ig beta subunits with affinities comparable to their binding to the TCR CD3 epsilon subunit (Kong 1995). Another feature that distinguish ZAP70 from Syk is its greater dependency on Src kinases for activation and its ability to phosphorylate and promote the auto-activation of the downstream mitogen-activated protein kinase (MAPK) p38 (reviewed in Au-Yeung 2009).

Mutations

Somatic

ZAP70 base mutation registry for ZAP70 deficiency. ZAP70 deficiency is a rare autosomal recessive form of severe combined immunodeficiency characterized by the selective absence of CD8+ T cells and by abundant CD4+ T cells in the peripheral blood that are unresponsive to TCR-mediated stimuli in vitro (http://bioinf.uta.fi/ZAP70base/index.php). The first rare ZAP70 mutations in humans were discovered before mouse models were established. The rare ZAP70 mutations in humans have been described in about 20 patients from different families (Arpaia 1994; Elder 1994; Chan 1994b; review in Fischer 2010 and Karaca 2013). All patients that were reported with complete deficiency in ZAP70 activity presented with severe clinical phenotype similar to severe combined immunodeficiency. ZAP70 mutations occurring in human SCID are mostly located in the kinase domain, but mutations causing transcriptional loss of ZAP70 or destabilization of the protein have also been reported. Elder et al reported that a patient with a missense mutation within the highly conserved DLAARN motif of the kinase domain (Elder 2001). Other examples are described by Fischer et al and by Karaca et al showing a lack or absence of CD8-positive T cells, high numbers of nonfunctional CD4-positive T cells, but normal numbers of B cells, with some patients having normal or elevated serum immunoglobulins (Ig) levels and defective antibody production (Matsuda 1999; Noraz 2000; Meinl 2000; Turul 2009; Picard 2009; review in Fischer 2010 and Karaca 2013).

Implicated in

Severe combined immunodeficiency (SCID)

Lack of ZAP70 in humans leads to a severe immunodeficiency characterized by the absence of CD8+ T-cells and TCR-unresponsive mature CD4+ T-cells. Mice lacking ZAP70 are also deficient in the production of CD4+ T-cells, while the natural killer cells are unaffected (Arpaia 1994; Elder 1994; Chan 1994b; Negishi 1995; reviewed in Mustelin 2003).
Roifman described in 1995 a new type of selective T-cell deficiency characterized by persistent infections reminiscent of severe combined immunodeficiency (Roifman 1995).
The patients carry a mutation of ZAP70, resulting in a loss of the kinase activity.
The study revealed that ZAP70 kinase appears to be indispensable for the development of CD8 single-positive T cells as well as for the signal transduction and function of single-positive CD4 T cells.
However, positive selection of CD4-positive T cells occurs in SCID patients, but the peripheral CD4-T cells do not respond normally to mitogens or to stimulation (Gelfand 1995).
The result of ZAP70 mutations in humans leading to SCID have been described in the section above.

Chronic lymphocytic leukemia (CLL)

ZAP70 was first thought to be uniquely expressed in T-cells, thymocytes and NK-cells. However, microarray analyses in CLL revealed that some B-

cells expressed ZAP70 (Rosenwald 2001). CLL is characterized by a clonal expansion of neoplastic CD19+, CD5+, CD23+ B-cells in the blood, bone marrow, lymph nodes and spleen (Chiorazzi 2005). The heterogenous clinical course identifies two subsets of patients that includes the levels of CD38, the mutational status of immunoglobulin (Ig) heavy chain variable regions (VH) and cytogenetic abnormalities. Indeed, ZAP70 was found to be most discriminating gene between the two subsets of CLL, with higher expression of ZAP70 in the unmutated IgVH CLL group (Rosenwald 2001). Several studies validated this finding and reported that ZAP70 predicted an unfavorable disease course in terms of disease progression and overall survival (Crespo 2003; Orchard 2004; Wiestner 2003; and review in Rodrïguez-Vicente 2013; Rosenquist 2013), but discordant results exists (Kröber 2006). It was also shown that ZAP70 is a better predictor of the need for treatment than IgVH status (Rassenti 2004). Chen et al showed early that expression of ZAP70 is associated with increased B-cell receptor signaling in CLL (Chen 2002), but it seems like the presence of ZAP70 in CLL is independent of its kinase activity (Chen 2008), suggesting that the function is more likely as an adaptor molecule to facilitate BCR signaling in CLL, or may compete for a negative regulator of Syk (review in Au-Yeung 2009). Rassenti et al showed in 2008 that ZAP70 levels can be used as an independent marker of clinical outcome in CLL (Rassenti 2008). The clinical course is correlated with augmented signaling down the BCR pathway, albeit not necessarily due to its enzymatic actions (Gobessi 2007; review in Chiorazzi 2012). It was also suggested that ZAP-70 retards internalization of surface membrane IgM and CD79b from the cell membrane, leading to prolonged BCR pathway signaling. An important component of ZAP-70 expression is indeed trafficking to solid tissue niches where signaling through chemokine receptors and BCRs might promote survival and further proliferation (Chiorazzi 2012). Many research groups are now focusing on the microenvironment and, for instance the role of chemokines, in the disease progress of CLL (review in Burger 2014 and Ten hacken 2015). The major CLL compartments in humans are lymph nodes (LN), bone marrow (BM) and peripheral blood (PB), which are, in different ways, giving stimuli to the neoplastic B cells. Different cell types such as stromal cells, nurselike cells and lymphoma associated macrophages will interact in a complex cross-talk with CLL cells, together with T cells and NK cells (Burger 2014). These cells communicate with the CLL cells through an extensive network of adhesion molecules, chemokine receptors, tumor necrosis factor (TNF) family members, and soluble factors (Ten hacken 2015), resulting in either increased or decreased clonal growth and downstream intracellular signaling.

Non-Hodgkin lymphoma

ZAP70 is expressed in malignant non-Hodgkin lymphoma (NHL) B-cell subsets, including precursor B-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma, mantle cell lymphoma, multiple myeloma, Hodgkin lymphoma and more(Sup 2004, Admirand 2004; Wang 2005; Carreras 2005; Scielzo 2006).

B-cell acute lymphoblastic leukemia (B-ALL)

ZAP-70 was consistently expressed and phosphorylated on Tyr319 in B-lineage ALL cells (Guillaume 2005). Crespo et al also found an expression of ZAP70 in 56% of B-ALL cases with pro/pre B cell phenotype (Crespo 2006), whereas childhood B-ALL showed even higher expression, in nine out of twelve cases (Wandroo 2008). In adult B-ALL, both less and more frequent ZAP70 expression can be detected (Wang 2005; Chakupurakal 2012).

Diffuse large B-cell lymphoma

ZAP70 was expressed in a significantly higher percentage of tumor cells in the clinically more aggressive non-germinal center (GC) group compared with the prognostically favourable GC group (Fridberg 2007).

Hodgkin lymphoma

ZAP70 is expressed in rare cases of classic Hodgkin lymphoma (Sup 2004) whereas two other independent studies did not detect any ZAP70-positive cells in Hodgkin lymphoma specimens (Admirand 2004; Carreras 2005).

Anaplastic large cell lymphoma

Anaplastic large cell lymphoma (ALCL) is a peripheral T cell lymphoma, often with defective expression of the TCR (Bonzheim 2004). Bonzheim et al showed that ZAP-70 was lacking in more than 70% of all ALCL cases studied. Altogether, the lack of CD3 and ZAP70 contribute to the dysregulation of intracellular signaling pathways controlling T cell activation and survival.

Rheumatoid arthritis

B cells play an important role in the pathogenesis of rheumatoid arthritis(RA). It has been shown that ZAP70 expression in synovial fluid B cells obtained from RA patients was increased compared to SF B cells of osteoarthritis patients (Tolusso 2009). Moreover, B cell apoptosis studied in vitro showed that the ZAP70- B cells spontaneously undergoing apoptosis were significantly higher than ZAP70+ B cells. The authors concluded that the presence of ZAP70+ B cells increased survival and local inflammation in RA (Tolusso 2009).

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