TNFAIP3 (tumor necrosis factor, alpha-induced protein 3)

Silvia Rasi, Davide Rossi, Gianluca Gaidano

Division of Hematology, Department of Clinical and Experimental Medicine & Center of Biotechnologies for Applied Medical Research, Amedeo Avogadro University of Eastern Piedmont, Via Solaroli 17, 28100 Novara, Italy (SR, DR, GG)

Published in Atlas Database: June 2009
Online updated version: http://AtlasGeneticsOncology.org/Genes/TNFAIP3Id42600ch6q23.html
DOI: 10.4267/2042/44762
This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2010 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names: A20; MGC104522; MGC138687; MGC138688; OTUD7C; TNFA1P2
HGNC (Hugo): TNFAIP3
Location: 6q23.3
Local order: TNFAIP3 is located on chromosome 6 on the long arm (forward strand), and lies between the PERP (PERP, TP53 apoptosis effector) and OLIG3 (oligodendrocyte transcription factor 3) genes.

Note
TNFAIP3 is a gene whose expression is induced by TNF (tumor necrosis factor). TNFAIP3 encodes a cytoplasmatic zinc finger protein that inhibits NFκB (nuclear factor of kappa light polypeptide gene enhancer in B-cells) activation and TNF-mediated apoptosis. Studies in knockout mice show that TNFAIP3 is important for limiting inflammation by terminating TNF-induced NFκB responses.

DNA/RNA

Description
TNFAIP3 is a functioning gene of 15869 bp comprising 9 exons and 8 introns. Exon 1, the 5’ part of exon 2 and the 3’ part of exon 9 are non coding.

Transcription
Length of the transcript is 4446 bp.
Coding sequence: CDS 67-2439.
mRNA is expressed at high levels in lymph nodes, respiratory tract, larynx, trachea and kidney.

A. Chromosomal location of TNFAIP3 gene.
B. Mapping of TNFAIP3 gene and local order on genomic context of the chromosome 6.
Protein

**Description**
Protein length of the unprocessed precursor: 790 amino acids.
Molecular weight of the unprocessed precursor: 89614 Da.
TNFAIP3 is a zinc finger protein containing seven A20-type finger motifs (E3 ubiquitin ligase domain) in its C-terminal region and a deubiquitinating enzyme domain, termed ovarian tumor (OTU) domain, in its N-terminal region. TNFAIP3 belongs to the peptidase C64 family. It is a homodimer that interacts with:
- TNIP1 (TNFAIP3 interacting protein 1, also known as Naf1 or ABIN-1),
- TAX1BP1 (Tax1 binding protein 1, also known as TXBP151 or T6BP),
- ITCH (itchy E3 ubiquitin protein ligase homolog (mouse)),
- RNF11 (ring finger protein 11),
- TRAF1, TRAF2, TRAF6 (TNF receptor-associated protein 1, 2 and 6).

**Expression**
Expression of TNFAIP3 is induced by TNF and is repressed by PML (promyelocytic leukemia) protein.

**Localisation**
Cytoplasm and nucleus.

**Function**
TNFAIP3 inhibits activation of NFKB and AP-1 transcription factors, and TNF- and IL-1beta (interleukin-1beta)-induced apoptosis.
TNFAIP3 is critical for limiting inflammatory processes by terminating TNF-induced NFKB responses, and contributes to the in vivo effects of TNF.
TNFAIP3 also restricts NFKB signaling in response to stimulation of TLR (toll-like receptor) and NOD (nuclear-binding and oligomerization domain) pathways.

TNFAIP3 possesses dual ubiquitin-editing functions. In particular, the N-terminal domain of TNFAIP3 is a deubiquitinating enzyme (DUB) for Lys63-linked polyubiquitinated signaling mediators such as TRAF2/6 and RIP1 (receptor interacting protein 1). Instead, the C-terminal domain of TNFAIP3 is a ubiquitin ligase (E3) for Lys48-linked degradative polyubiquitination of the same substrates. TNFAIP3 has a specificity for particular polyubiquitinated substrates to regulate NFKB activation in the TNF, IL-1beta and TLR pathways.

TNFAIP3 has a role in the function of the lymphoid system because it inhibits NFKB signaling and may play an important role in lymphomagenesis. TNFAIP3 also negatively regulates the activity of CARD10 (caspase recruitment domain family, member 10) and BCL10 (B-cell CLL/lymphoma 10) in lymphoid and non-lymphoid cells.

A TNFAIP3-mediated inhibition of TNF-induced apoptosis is associated with the inhibition of caspase-8. TNFAIP3 acts forming a multiprotein complex with other proteins, in particular ABIN-1, TAX1BP1, ITCH, RNF11, TRAF1, TRAF2, TRAF6, to regulate NFKB signaling cascade and TNF-induced cell death.
TNFAIP3 negatively regulates the maturation, inflammatory cytokine production and immunostimulatory potency of dendritic cells.

**Homology**
Interspecies: ortholog to murine TNFAIP3 and homolog to Caenorhabditis elegans F21C3.2.

**Mutations**
**Somatic**
Deletions and bi-allelic somatic mutations involving TNFAIP3 gene have been identified in different subtypes of B-cell lymphomas. Most of the TNFAIP3
mutations are nonsense or frameshift that prevent production of full-length TNFAIP3 protein.

**Implicated in**

**Marginal Zone B-cell Lymphoma (MZBCL)**

**Disease**
The incidence of MZBCL in the Western world is approximately 10% of all non-Hodgkin’s lymphomas (NHLs). MZBCL includes three distinct clinicopathological forms: 1- Extraneural MZBCL of mucosa-associated lymphoid tissue (MALT) type, 2- Splenic MZBCL, 3- Nodal MZBCL. The TNFAIP3 gene, that is a common genetic target in B-cell lymphomas, is frequently inactivated by somatic mutations and/or deletions in MALT lymphoma. Homozygous deletions of the chromosomal band 6q23, involving the TNFAIP3 gene, were identified in ocular adnexal MZBCLs. Inactivating mutations encoding truncated TNFAIP3 protein were also identified in extraneural, nodal and splenic MZBCLs.

**Prognosis**
The patients usually have prolonged survival, but some cases may feature an aggressive disease. In ocular adnexal MZBCLs, TNFAIP3 deletion appears to be associated with adverse clinical parameters and with concurrent involvement of different adnexal tissues or extraocular sites at diagnosis. TNFAIP3 deletion is also associated with a higher proportion of relapse and with a shorter relapse-free survival.

**Oncogenesis**
TNFAIP3 inactivation by somatic mutation and/or deletion represents a genetic aberration across all MZBCL subtypes, which may contribute to lymphomagenesis by inducing constitutive NFKB activation. This suggests that TNFAIP3 may act as a tumor suppressor gene in MZBCLs.

**Classical Hodgkin’s Lymphoma (cHL)**

**Disease**
cHL is a disease that involves a clonal expansion of neoplastic B lymphocytes. A constitutive NFKB activity has been detected in cHL and somatic mutations have been identified in the TNFAIP3 gene. Both TNFAIP3 alleles are inactivated, with frequent chromosomal deletion of TNFAIP3. Reconstitution of wild-type protein in TNFAIP3-deficient cHL cell lines results in a downregulation of NFKB activity and in suppression of cell growth with induction of apoptosis. In fact TNFAIP3-deficient cells generate tumours in immunodeficient mice, whereas the re-expression of TNFAIP3 suppresses the tumorigenicity.

**Oncogenesis**
TNFAIP3 has been identified in cHL, as in other B-cell lymphomas, as a tumor suppressor gene. Loss of TNFAIP3 function, inducing a constitutive activity of NFKB, is probably involved in the pathogenesis of cHL.

**Diffuse Large B-cell Lymphoma (DLBCL)**

**Disease**
DLBCL is the most common type of lymphoma in adulthood and is a heterogeneous disease, with patients exhibiting a wide range of clinical variables, outcomes and responses to therapy. In fact DLBCL includes different biologically and clinically distinct subtypes: - Germinol centre B-cell-like (GCB) DLBCL, - Activated B-cell-like (ABC) DLBCL. ABC-DLBCL, that is the most aggressive subtype, is associated with constitutive activation of NFKB. ABC-DLBCL and a smaller fraction of GCB-DLBCL carry somatic mutations in TNFAIP3 gene. In fact, approximately 30% of patients display biallelic inactivation of TNFAIP3 by mutations and/or deletions. Reconstitution of TNFAIP3 induces apoptosis and cell growth arrest, indicating a tumour suppressor role of the gene.

**Oncogenesis**
NFKB activation in DLBCL is caused by genetic lesions affecting multiple genes, including TNFAIP3. Alterations of these genes may promote lymphomagenesis by leading to abnormally prolonged NFKB responses.

**Primary Mediastinal B-cell Lymphoma (PMBL)**

**Disease**
PMBL is a subtype of DLBCL defined by a combination of clinical and pathologic features. PMBL typically presents in young female patients, that have bulky mediastinal masses with frequent invasion of adjacent structures. PMBL is a lymphoma with constitutive NFKB activity and significantly high frequency of TNFAIP3 mutations.

**Oncogenesis**
TNFAIP3 has been identified as a tumor suppressor gene in PMBL by showing frequent somatic and clonal biallelic inactivation of the gene. Loss of TNFAIP3 function contributes to the constitutive activity of the transcription factor NFKB and the survival and/or proliferation of the cells.

**Breast cancer**

**Disease**
Breast cancer is the most common cancer among women in developed countries. The etiology is multifactorial and the majority of these tumors express estrogen receptor (ER). Tamoxifen has been shown to be an effective adjuvant therapy for ER+ tumors, but only 60% of ER+ tumors respond to this therapy.
TNFAIP3 is overexpressed in breast cancer cells and confers resistance to tamoxifen-induced cytotoxicity.

**Prognosis**

TNFAIP3 represents a potential prognostic marker of breast cancer, because an increased expression of TNFAIP3 is associated with an aggressive phenotype of the disease.

**Oncogenesis**

TNFAIP3 is probably a key protein involved in tamoxifen resistance in breast cancer because it is overexpressed in tamoxifen-resistant cell lines. It is a possible target for developing new strategies to prevent drug resistance in breast cancer.

**Nasopharyngeal carcinoma (NPC)**

**Disease**

TNFAIP3 expression is correlated with the differentiation stages of NPC. In particular, TNFAIP3 expression contributes to the development of undifferentiated NPC as well as poorly differentiated head and neck squamous cell carcinomas (SCCs).

**Oncogenesis**

TNFAIP3 may have a role in the pathogenesis and aggressiveness of these tumors, probably because TNFAIP3 is implicated in survival pathways.

**References**


This article should be referenced as such: