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Gene Section
Review

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

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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 NFKB (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 NFKB responses.

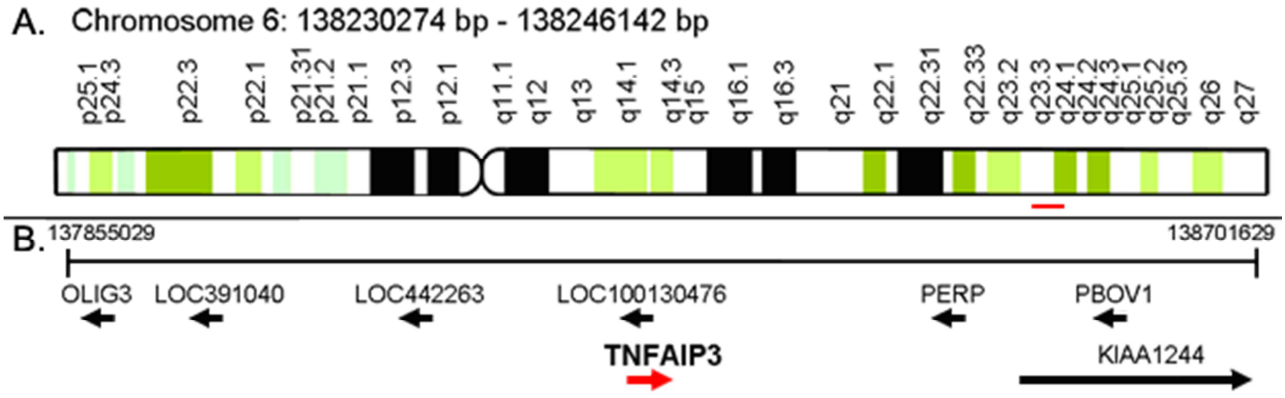
DNA/RNA

Description

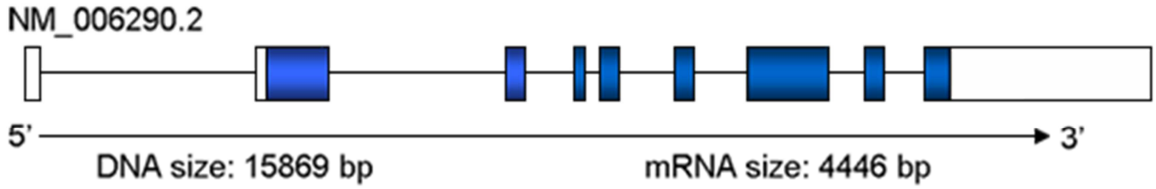
TNFAIP3 is a functioning gene of 15869 bp comprising 9 exons and 8 introns. Exon 1, the 5' part of exon 2 and the 3' part of exon 9 are non coding.

Transcription

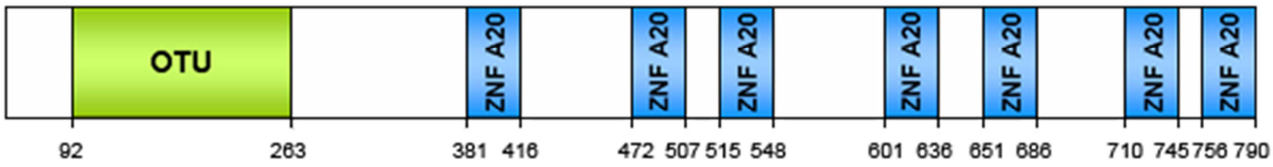
Length of the transcript is 4446 bp.
Coding sequence: CDS 67-2439.
mRNA is expressed at high levels in lymph nodes, respiratory tract, larynx, trachea and kidney.



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



Exon-intron structure of the TNFAIP3 gene. Blue boxes correspond to protein coding regions, while white boxes correspond to non coding regions.



Representation of the TNFAIP3 protein with localization of recognized domains. The ovarian tumor domain (OTU) is shown in green, while the seven zinc finger structures (ZNF A20) are shown in blue (UniProtKB/Swiss-Prot entry P21580).

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 factor 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- Extranodal 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 extranodal, 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:
- Germinal 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 adjiuvant 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

TNFAPI3 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

Dixit VM, Green S, Sarma V, Holzman LB, Wolf FW, O'Rourke K, Ward PA, Prochownik EV, Marks RM. Tumor necrosis factor-alpha induction of novel gene products in human endothelial cells including a macrophage-specific chemotaxin. J Biol Chem. 1990 Feb 15;265(5):2973-8

Opipari AW Jr, Boguski MS, Dixit VM. The A20 cDNA induced by tumor necrosis factor alpha encodes a novel type of zinc finger protein. J Biol Chem. 1990 Sep 5;265(25):14705-8

Opipari AW Jr, Hu HM, Yabkowitz R, Dixit VM. The A20 zinc finger protein protects cells from tumor necrosis factor cytotoxicity. J Biol Chem. 1992 Jun 25;267(18):12424-7

Cooper JT, Stroka DM, Brostjan C, Palmetshofer A, Bach FH, Ferran C. A20 blocks endothelial cell activation through a NF-kappaB-dependent mechanism. J Biol Chem. 1996 Jul 26;271(30):18068-73

Jäättelä M, Mouritzen H, Elling F, Bastholm L. A20 zinc finger protein inhibits TNF and IL-1 signaling. J Immunol. 1996 Feb 1;156(3):1166-73

Song HY, Rothe M, Goeddel DV. The tumor necrosis factor-inducible zinc finger protein A20 interacts with TRAF1/TRAF2 and inhibits NF-kappaB activation. Proc Natl Acad Sci U S A. 1996 Jun 25;93(13):6721-5

Srinivasan A, Li F, Wong A, Kodandapani L, Smidt R Jr, Krebs JF, Fritz LC, Wu JC, Tomaselli KJ. Bcl-xL functions downstream of caspase-8 to inhibit Fas- and tumor necrosis factor receptor 1-induced apoptosis of MCF7 breast carcinoma cells. J Biol Chem. 1998 Feb 20;273(8):4523-9

Codd JD, Salisbury JR, Packham G, Nicholson LJ. A20 RNA expression is associated with undifferentiated nasopharyngeal carcinoma and poorly differentiated head and neck squamous cell carcinoma. J Pathol. 1999 Apr;187(5):549-55

De Valck D, Jin DY, Heyninck K, Van de Craen M, Contreras R, Fiers W, Jeang KT, Beyaert R. The zinc finger protein A20 interacts with a novel anti-apoptotic protein which is cleaved by specific caspases. Oncogene. 1999 Jul 22;18(29):4182-90

Grey ST, Arvelo MB, Hasenkamp W, Bach FH, Ferran C. A20 inhibits cytokine-induced apoptosis and nuclear factor kappaB-dependent gene activation in islets. J Exp Med. 1999 Oct 18;190(8):1135-46

Heyninck K, De Valck D, Vanden Berghe W, Van Criekinge W, Contreras R, Fiers W, Haegeman G, Beyaert R. The zinc finger protein A20 inhibits TNF-induced NF-kappaB-dependent gene expression by interfering with an RIP- or TRAF2-mediated transactivation signal and directly binds to a novel NF-kappaB-inhibiting protein ABIN. J Cell Biol. 1999 Jun 28;145(7):1471-82

Beyaert R, Heyninck K, Van Huffel S. A20 and A20-binding proteins as cellular inhibitors of nuclear factor-kappa B-dependent gene expression and apoptosis. Biochem Pharmacol. 2000 Oct 15;60(8):1143-51

Lee EG, Boone DL, Chai S, Libby SL, Chien M, Lodolce JP, Ma A. Failure to regulate TNF-induced NF-kappaB and cell death responses in A20-deficient mice. Science. 2000 Sep 29;289(5488):2350-4

Lademann U, Kallunki T, Jäättelä M. A20 zinc finger protein inhibits TNF-induced apoptosis and stress response early in the signaling cascades and independently of binding to TRAF2 or 14-3-3 proteins. Cell Death Differ. 2001 Mar;8(3):265-72

Boone DL, Turer EE, Lee EG, Ahmad RC, Wheeler MT, Tsui C, Hurley P, Chien M, Chai S, Hitotsumatsu O, McNally E, Pickart C, Ma A. The ubiquitin-modifying enzyme A20 is required for termination of Toll-like receptor responses. Nat Immunol. 2004 Oct;5(10):1052-60

Evans PC, Ovaa H, Hamon M, Kilshaw PJ, Hamm S, Bauer S, Ploegh HL, Smith TS. Zinc-finger protein A20, a regulator of inflammation and cell survival, has de-ubiquitinating activity. Biochem J. 2004 Mar 15;378(Pt 3):727-34

Meylan E, Burns K, Hofmann K, Blancheteau V, Martinon F, Kelliher M, Tschopp J. RIP1 is an essential mediator of Toll-like receptor 3-induced NF-kappa B activation. Nat Immunol. 2004 May;5(5):503-7

Wang YY, Li L, Han KJ, Zhai Z, Shu HB. A20 is a potent inhibitor of TLR3- and Sendai virus-induced activation of NF-kappaB and ISRE and IFN-beta promoter. FEBS Lett. 2004 Oct 8;576(1-2):86-90

Wertz IE, O'Rourke KM, Zhou H, Eby M, Aravind L, Seshagiri S, Wu P, Wiesmann C, Baker R, Boone DL, Ma A, Koonin EV, Dixit VM. De-ubiquitination and ubiquitin ligase domains of A20 downregulate NF-kappaB signalling. Nature. 2004 Aug 5;430(7000):694-9

Chen ZJ. Ubiquitin signalling in the NF-kappaB pathway. Nat Cell Biol. 2005 Aug;7(8):758-65

Cusson-Hermance N, Khurana S, Lee TH, Fitzgerald KA, Kelliher MA. Rip1 mediates the Trif-dependent toll-like receptor 3- and 4-induced NF-{kappa}B activation but does not contribute to interferon regulatory factor 3 activation. J Biol Chem. 2005 Nov 4;280(44):36560-6

Heyninck K, Beyaert R. A20 inhibits NF-kappaB activation by dual ubiquitin-editing functions. Trends Biochem Sci. 2005 Jan;30(1):1-4

Saitoh T, Yamamoto M, Miyagishi M, Taira K, Nakanishi M, Fujita T, Akira S, Yamamoto N, Yamaoka S. A20 is a negative regulator of IFN regulatory factor 3 signaling. J Immunol. 2005 Feb 1;174(3):1507-12

Lin R, Yang L, Nakhaei P, Sun Q, Sharif-Askari E, Julkunen I, Hiscott J. Negative regulation of the retinoic acid-inducible gene I-induced antiviral state by the ubiquitin-editing protein A20. J Biol Chem. 2006 Jan 27;281(4):2095-103

Vendrell JA, Ghayad S, Ben-Larbi S, Dumontet C, Mechti N, Cohen PA. A20/TNFAIP3, a new estrogen-regulated gene that confers tamoxifen resistance in breast cancer cells. Oncogene. 2007 Jul 12;26(32):4656-67

Bibeau-Poirier A, Servant MJ. Roles of ubiquitination in pattern-recognition receptors and type I interferon receptor signaling. Cytokine. 2008 Sep;43(3):359-67

Hitotsumatsu O, Ahmad RC, Tavares R, Wang M, Philpott D, Turer EE, Lee BL, Shiffin N, Advincula R, Malynn BA, Werts C, Ma A. The ubiquitin-editing enzyme A20 restricts nucleotide-binding oligomerization domain containing 2-triggered signals. Immunity. 2008 Mar;28(3):381-90

Honma K, Tsuzuki S, Nakagawa M, Karnan S, Aizawa Y, Kim WS, Kim YD, Ko YH, Seto M. TNFAIP3 is the target gene of chromosome band 6q23.3-q24.1 loss in ocular adnexal marginal zone B cell lymphoma. Genes Chromosomes Cancer. 2008 Jan;47(1):1-7

Lin SC, Chung JY, Lamothe B, Rajashankar K, Lu M, Lo YC, Lam AY, Darnay BG, Wu H. Molecular basis for the unique deubiquitinating activity of the NF-kappaB inhibitor A20. J Mol Biol. 2008 Feb 15;376(2):526-40

Shembade N, Harhaj NS, Parvatiyar K, Copeland NG, Jenkins NA, Matesic LE, Harhaj EW. The E3 ligase Itch negatively regulates inflammatory signaling pathways by controlling the function of the ubiquitin-editing enzyme A20. Nat Immunol. 2008 Mar;9(3):254-62

Song XT, Evel-Kabler K, Shen L, Rollins L, Huang XF, Chen SY. A20 is an antigen presentation attenuator, and its inhibition overcomes regulatory T cell-mediated suppression. Nat Med. 2008 Mar;14(3):258-65

Stilo R, Varricchio E, Liguoro D, Leonardi A, Vito P. A20 is a negative regulator of BCL10- and CARMA3-mediated activation of NF-kappaB. J Cell Sci. 2008 Apr 15;121(Pt 8):1165-71

Thelander EF, Ichimura K, Corcoran M, Barbany G, Nordgren A, Heyman M, Berglund M, Mungall A, Rosenquist R, Collins VP, Grandér D, Larsson C, Lagercrantz S. Characterization of 6q deletions in mature B cell lymphomas and childhood acute lymphoblastic leukemia. Leuk Lymphoma. 2008 Mar;49(3):477-87

Chanudet E, Ye H, Ferry J, Bacon CM, Adam P, Müller-Hermelink HK, Radford J, Pileri SA, Ichimura K, Collins VP, Hamoudi RA, Nicholson AG, Wotherspoon AC, Isaacson PG, Du MQ. A20 deletion is associated with copy number gain at the TNFA/B/C locus and occurs preferentially in translocation-negative MALT lymphoma of the ocular adnexa and salivary glands. J Pathol. 2009 Feb;217(3):420-30

Compagno M, Lim WK, Grunn A, Nandula SV, Brahmachary M, Shen Q, Bertoni F, Ponzoni M, Scandurra M, Califano A, Bhagat G, Chadburn A, Dalla-Favera R, Pasqualucci L. Mutations of multiple genes cause deregulation of NF-kappaB in diffuse large B-cell lymphoma. Nature. 2009 Jun 4;459(7247):717-21

Kato M, Sanada M, Kato I, Sato Y, Takita J, Takeuchi K, Niwa A, Chen Y, Nakazaki K, Nomoto J, Asakura Y, Muto S, Tamura A, Iio M, Akatsuka Y, Hayashi Y, Mori H, Igarashi T, Kurokawa M, Chiba S, Mori S, Ishikawa Y, Okamoto K, Tobinai K, Nakagama H, Nakahata T, Yoshino T, Kobayashi Y, Ogawa S. Frequent inactivation of A20 in B-cell lymphomas. Nature. 2009 Jun 4;459(7247):712-6

Malynn BA, Ma A. A20 takes on tumors: tumor suppression by an ubiquitin-editing enzyme. J Exp Med. 2009 May 11;206(5):977-80

Novak U, Rinaldi A, Kwee I, Nandula SV, Rancoita PM, Compagno M, Cerri M, Rossi D, Murty VV, Zucca E, Gaidano G, Dalla-Favera R, Pasqualucci L, Bhagat G, Bertoni F. The NF-{kappa}B negative regulator TNFAIP3 (A20) is inactivated by somatic mutations and genomic deletions in marginal zone lymphomas. Blood. 2009 May 14;113(20):4918-21

Schmitz R, Hansmann ML, Bohle V, Martin-Subero JI, Hartmann S, Mechtersheimer G, Klapper W, Vater I, Giefing M, Gesk S, Stanelle J, Siebert R, Küppers R. TNFAIP3 (A20) is a tumor suppressor gene in Hodgkin lymphoma and primary mediastinal B cell lymphoma. J Exp Med. 2009 May 11;206(5):981-9

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