Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

GZMA (granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3))

Elena Catalan, Diego Sanchez-Martinez, Julián Pardo

Dpto Bioquimica y Biologia Molecular y Celular, Fac Ciencias, Univ Zaragoza, Spain (EC, DSM), Dpto Bioquimica y Biologia Molecular y Celular, Fac Ciencias, Univ Zaragoza, Spain; Fundacion Aragon I+D (ARAID), Zaragoza, Spain (JP)

Published in Atlas Database: September 2011

Online updated version : http://AtlasGeneticsOncology.org/Genes/GZMAID51130ch5q11.html
DOI: 10.4267/2042/46942

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© *2012 Atlas of Genetics and Cytogenetics in Oncology and Haematology*

Identity

Other names: CTLA3, HFSP

HGNC (Hugo): GZMA

Location: 5q11.2

Local order: Size: 7607 bases. Coordinates: 54398473.

DNA/RNA

Description

The GZMA gene, with 7607 bases in length, consists of 5 exons and 4 introns. GZMA gene is located in a gene cluster together with granzyme K (figure 1) (Grossman et al., 2003).

Transcription

There are at least two transcripts of human GZMA whose expression is differentially regulated by glucocorticoid (Ruike et al., 2007). These transcripts generate two isoforms, GZMAα and GZMAβ, which have respective first exons: exon 1a and exon 1b (figure 1):
GZMAα (exon 1a): canonical sequence,
GZMAβ (exon 1b): lack aa 1-17; aa 18-23 LLLIPE --> MTKGLR.

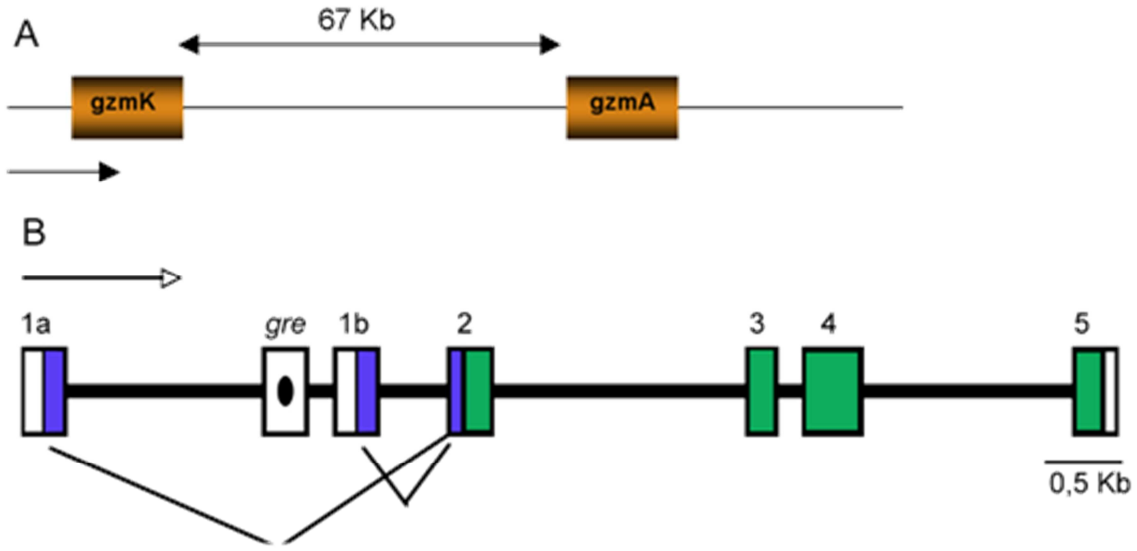

Figure 1. Genomic organization of human GZMA. A, human GZMA cluster. Arrow indicate the direction of transcription. **B**, representation of the GZMA genetic locus. White: untranslated regions; Blue: leader sequence; Green: mature enzyme. Solid lanes: splicing between the first and second exons. gre: glucocorticoid response element (adapted from Ruike et al., 2007).

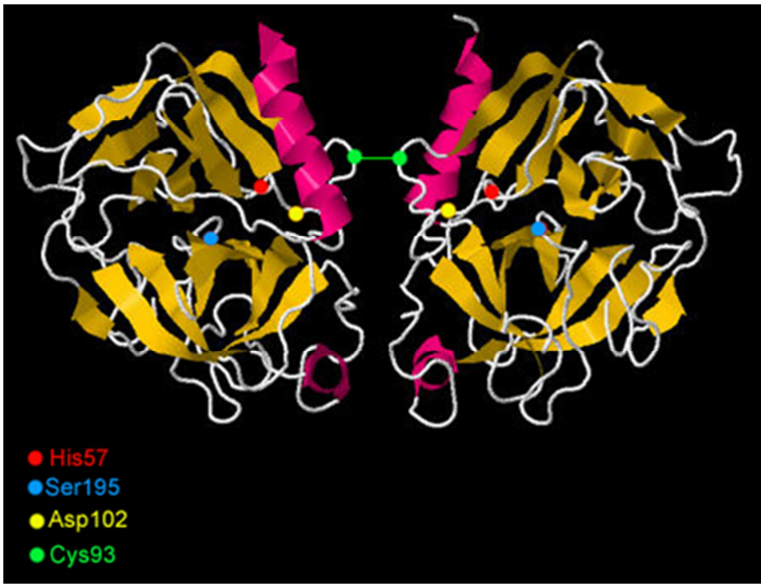

Figure 2. Diagram of the crystal structure of human granzyme A dimer (Bell et al., 2003; Hink-Schauer et al., 2003). The cystein groups involved in disulphide bond-mediated dimer (green) and the three aminoacids forming the catalytic triad (red, blue and yellow) are shown. Representation from PDB (accession code 1OP8) deposited by Hink-Schauer C, Estébanez-Perpiñá E, Kurschus FC, Bode W, Jenne DE. Nat Struct Biol. 2003 Jul;10(7):535-40.

Protein

Description

Granzyme A is a tryptase (cleave proteins after Lys or Arg residues) expressed mainly in cytotoxic cells (cytotoxic T and Natural Killer cells) (Masson et al., 1986; Simon et al., 1986; Young et al., 1986). Protein is expressed as a preproenzyme (Jenne et al., 1988) containing a signal sequence that mediates targeting of the nascent enzyme to the ER. Cleavage of the signal peptide produces an inactive proenzyme that contains an N-terminal dipeptide that needs to be cleaved to produce an active protease. In the Golgi, a mannose-6-phosphate tag is added for transporting the proenzyme to cytotoxic granules. Within the cytotoxic granule, the N-terminal dipeptide is removed by cathepsin C (dipeptidyl peptidase I) (Pham et al., 1999), producing the active enzyme that is kept inactive at low pH. Native granzyme A is expressed as a dimer (Bell et al., 2003; Hink-Schauer et al., 2003).

Expression

Cytotoxic CD8+ T cells, Natural Killer cells, CD4+ T cells, gamma-delta T cells, type II pneumocytes, alveolar macrophages, bronchiolar epithelial cells.

Localisation

Cytotoxic granules.

Function

Granzyme A is delivered from CTL or NK cytotoxic granules to the cytoplasm of target cell by a mechanism dependent on perforin (Baran et al., 2009; Praper et al., 2011; Thiery et al., 2011).

There are some controversial findings about the physiological function of gzmA.

It has been reported that human GzmA induces perforin-mediated caspase-independent cell death in some tumors cell lines (Hayes et al., 1989; Shi et al., 1992; Beresford et al., 1999; Shresta et al., 1999; Pardo et al., 2004). GzmA translocates to the nucleus and mitochondria where key substrates such as mitochondrial complex I protein, NADH dehydrogenase Fe-S protein 3 (NDUFS3) is cleaved, inducing the production of Radical Oxygen Species (ROS). ROS production induces the activation of the SET complex that translocates into the nucleus in order to repair DNA damage induced by ROS. Once there, granzyme A cleaves components of the endoplasmic reticulum-associated SET complex, releasing the endonuclease NM23H1 that induces single strand nicks in the DNA and ultimately cell death (Lieberman, 2011).

Other authors have reported that the cytotoxic potential of granzyme A is low, but induce expression of pro-inflammatory cytokines in monocytes-like cells by a caspase-1 dependent mechanism (Metkar et al., 2008).

Granzyme A is able to cleave several extracellular substrates like thrombin receptor, fibronectin, collagen IV, proteinase-activated receptor-2, Pro-urokinase plasminogen activator and myelin basic protein (Kramer et al., 1987; Buzza et al., 2006; Hendel et al., 2011).

Granzyme and granzyme B double deficient mice are more susceptible than granzyme B deficient mice to transplanted tumors suggesting a contribution of granzyme A to tumor control in vivo (Pardo et al., 2002; Cao et al., 2007).

Homology

Mouse granzyme A; Rat granzyme A; Chicken granzyme A; Fish granzyme A (Common Carp, Atlantic cod, Channel catfish) (Praveen et al., 2006; Praveen et al., 2006; Wernersson et al., 2006).

Mutations

Note: Not known.

Implicated in

Sepsis (Froelich et al., 2009; Hendel et al., 2011)

Disease

Several findings suggest that gzmA contributes to septic shock. Native and recombinant human granzyme A as well as a human NK cell line expressing gzmA induces human adherent peripheral blood mononuclear cells to express proinflammatory cytokines including interleukin-1beta interleukin-6, inteleukin-8 and TNF-alpha (Sower et al., 1996; Metkar et al., 2008). Granzyme A deficient mice are more resistant than wild type mice to septic shock induced by LPS (Metkar et al., 2008).

Rheumatoid arthritis

Prognosis

Granzyme A levels are higher in serum and synovial fluid of patients with rheumatoid arthritis (Griffiths et al., 1992; Nordstrom et al., 1992; Kummer et al., 1994; Tak et al., 1994; Muller-Ladner et al., 1995; Spaeny-Dekking et al., 1998; Tak et al., 1999).

Chronic obstructive pulmonary disease

Prognosis

Granzyme A is expressed in type II pneumocytes of patients with severe chronic obstructive pulmonary disease (Vernooy et al., 2007).

Hypersensitivity pneumonitis

Prognosis

Granzyme A is elevated in bronchoalveolar lavage fluid from patients with hypersensitivity pneumonitis (Tremblay et al., 2000).

Sjögren's syndrome

Prognosis

Granzyme A is expressed in salivary glands from patients with Sjögren's syndrome (Alpert et al., 1994).

Poxvirus infection

Disease

Granzyme A deficient mice are more susceptible than wild type mice to mousepox virus (ectromelia) (Mullbacher et al., 1996).

Herpes virus infection

Disease

Granzyme A deficient mice are more susceptible than wild type mice to herpes simplex virus type 1 (HSV-1) (Pereira et al., 2000) and mouse cytomegalovirus (CMV) infection (Riera et al., 2000).

References

Masson D, Zamai M, Tschopp J. Identification of granzyme A isolated from cytotoxic T-lymphocyte-granules as one of the proteases encoded by CTL-specific genes. FEBS Lett. 1986 Nov 10;208(1):84-8

Simon MM, Hoschützky H, Fruth U, Simon HG, Kramer MD. Purification and characterization of a T cell specific serine proteinase (TSP-1) from cloned cytolytic T lymphocytes. EMBO J. 1986 Dec 1;5(12):3267-74

Young JD, Hengartner H, Podack ER, Cohn ZA. Purification and characterization of a cytolytic pore-forming protein from granules of cloned lymphocytes with natural killer activity. Cell. 1986 Mar 28;44(6):849-59

Kramer MD, Simon MM. Are Proteinases Functional Molecules of T Lymphocytes? Immunol Today. 1987;8:140-2. (REVIEW)

Jenne DE, Tschopp J.. Granzymes, a family of serine proteases released from granules of cytolytic T lymphocytes upon T cell receptor stimulation. Immunol Rev. 1988 Mar;103:53-71. (REVIEW)

Hayes MP, Berrebi GA, Henkart PA.. Induction of target cell DNA release by the cytotoxic T lymphocyte granule protease granzyme A. J Exp Med. 1989 Sep 1;170(3):933-46.

Griffiths GM, Alpert S, Lambert E, McGuire J, Weissman IL.. Perforin and granzyme A expression identifying cytolytic lymphocytes in rheumatoid arthritis. Proc Natl Acad Sci U S A. 1992 Jan 15;89(2):549-53.

Nordstrom DC, Konttinen YT, Sorsa T, Nykanen P, Pettersson T, Santavirta S, Tschopp J.. Granzyme A-immunoreactive cells in synovial fluid in reactive and rheumatoid arthritis. Clin Rheumatol. 1992 Dec;11(4):529-32.

Shi L, Kraut RP, Aebersold R, Greenberg AH.. A natural killer cell granule protein that induces DNA fragmentation and apoptosis. J Exp Med. 1992 Feb 1;175(2):553-66.

Alpert S, Kang HI, Weissman I, Fox RI.. Expression of granzyme A in salivary gland biopsies from patients with primary Sjogren's syndrome. Arthritis Rheum. 1994 Jul;37(7):1046-54.

Kummer JA, Tak PP, Brinkman BM, van Tilborg AA, Kamp AM, Verweij CL, Daha MR, Meinders AE, Hack CE, Breedveld FC.. Expression of granzymes A and B in synovial tissue from patients with rheumatoid arthritis and osteoarthritis. Clin Immunol Immunopathol. 1994 Oct;73(1):88-95.

Tak PP, Kummer JA, Hack CE, Daha MR, Smeets TJ, Erkelens GW, Meinders AE, Kluin PM, Breedveld FC.. Granzyme-positive cytotoxic cells are specifically increased in early rheumatoid synovial tissue. Arthritis Rheum. 1994 Dec;37(12):1735-43.

Muller-Ladner U, Kriegsmann J, Tschopp J, Gay RE, Gay S.. Demonstration of granzyme A and perforin messenger RNA in the synovium of patients with rheumatoid arthritis. Arthritis Rheum. 1995 Apr;38(4):477-84.

Mullbacher A, Ebnet K, Blanden RV, Hla RT, Stehle T, Museteanu C, Simon MM.. Granzyme A is critical for recovery of mice from infection with the natural cytopathic viral pathogen, ectromelia. Proc Natl Acad Sci U S A. 1996 Jun 11;93(12):5783-7.

Sower LE, Klimpel GR, Hanna W, Froelich CJ.. Extracellular activities of human granzymes. I. Granzyme A induces IL6 and IL8 production in fibroblast and epithelial cell lines. Cell Immunol. 1996 Jul 10;171(1):159-63.

Spaeny-Dekking EH, Hanna WL, Wolbink AM, Wever PC, Kummer JA, Swaak AJ, Middeldorp JM, Huisman HG, Froelich CJ, Hack CE.. Extracellular granzymes A and B in humans: detection of native species during CTL responses in vitro and in vivo. J Immunol. 1998 Apr 1;160(7):3610-6.

Beresford PJ, Xia Z, Greenberg AH, Lieberman J.. Granzyme A loading induces rapid cytolysis and a novel form of DNA damage independently of caspase activation. Immunity. 1999 May;10(5):585-94.

Pham CT, Ley TJ.. Dipeptidyl peptidase I is required for the processing and activation of granzymes A and B in vivo. Proc Natl Acad Sci U S A. 1999 Jul 20;96(15):8627-32.

Shresta S, Graubert TA, Thomas DA, Raptis SZ, Ley TJ.. Granzyme A initiates an alternative pathway for granule-mediated apoptosis. Immunity. 1999 May;10(5):595-605.

Tak PP, Spaeny-Dekking L, Kraan MC, Breedveld FC, Froelich CJ, Hack CE.. The levels of soluble granzyme A and B are elevated in plasma and synovial fluid of patients with rheumatoid arthritis (RA). Clin Exp Immunol. 1999 May;116(2):366-70.

Pereira RA, Simon MM, Simmons A.. Granzyme A, a noncytolytic component of CD8(+) cell granules, restricts the spread of herpes simplex virus in the peripheral nervous systems of experimentally infected mice. J Virol. 2000 Jan;74(2):1029-32.

Riera L, Gariglio M, Valente G, Mullbacher A, Museteanu C, Landolfo S, Simon MM.. Murine cytomegalovirus replication in salivary glands is controlled by both perforin and granzymes during acute infection. Eur J Immunol. 2000 May;30(5):1350-5.

Tremblay GM, Wolbink AM, Cormier Y, Hack CE.. Granzyme activity in the inflamed lung is not controlled by endogenous serine proteinase inhibitors. J Immunol. 2000 Oct 1;165(7):3966-9.

Pardo J, Balkow S, Anel A, Simon MM.. Granzymes are essential for natural killer cell-mediated and perf-facilitated tumor control. Eur J Immunol. 2002 Oct;32(10):2881-7.

Bell JK, Goetz DH, Mahrus S, Harris JL, Fletterick RJ, Craik CS.. The oligomeric structure of human granzyme A is a determinant of its extended substrate specificity. Nat Struct Biol. 2003 Jul;10(7):527-34.

Grossman WJ, Revell PA, Lu ZH, Johnson H, Bredemeyer AJ, Ley TJ.. The orphan granzymes of humans and mice. Curr Opin Immunol. 2003 Oct;15(5):544-52.

Hink-Schauer C, Estebanez-Perpina E, Kurschus FC, Bode W, Jenne DE.. Crystal structure of the apoptosis-inducing human granzyme A dimer. Nat Struct Biol. 2003 Jul;10(7):535-40.

Pardo J, Bosque A, Brehm R, Wallich R, Naval J, Mullbacher A, Anel A, Simon MM.. Apoptotic pathways are selectively activated by granzyme A and/or granzyme B in CTL-mediated target cell lysis. J Cell Biol. 2004 Nov 8;167(3):457-68.

Buzza MS, Bird PI.. Extracellular granzymes: current perspectives. Biol Chem. 2006 Jul;387(7):827-37. (REVIEW)

Praveen K, Leary JH 3rd, Evans DL, Jaso-Friedmann L.. Molecular characterization and expression of a granzyme of an ectothermic vertebrate with chymase-like activity expressed in the cytotoxic cells of Nile tilapia (Oreochromis niloticus). Immunogenetics. 2006 Feb;58(1):41-55. Epub 2006 Feb 9.

Praveen K, Leary JH 3rd, Evans DL, Jaso-Friedmann L.. Nonspecific cytotoxic cells of teleosts are armed with multiple granzymes and other components of the granule exocytosis pathway. Mol Immunol. 2006 Mar;43(8):1152-62. Epub 2005 Aug 30.

Wernersson S, Reimer JM, Poorafshar M, Karlson U, Wermenstam N, Bengten E, Wilson M, Pilstrom L, Hellman L.. Granzyme-like sequences in bony fish shed light on the emergence of hematopoietic serine proteases during vertebrate evolution. Dev Comp Immunol. 2006;30(10):901-18. Epub 2005 Dec 27.

Cao X, Cai SF, Fehniger TA, Song J, Collins LI, Piwnica-Worms DR, Ley TJ.. Granzyme B and perforin are important for regulatory T cell-mediated suppression of tumor clearance. Immunity. 2007 Oct;27(4):635-46. Epub 2007 Oct 4.

Ruike Y, Katsuma S, Hirasawa A, Tsujimoto G.. Glucocorticoid-induced alternative promoter usage for a novel 5' variant of granzyme A. J Hum Genet. 2007;52(2):172-8. Epub 2006 Dec 19.

Vernooy JH, Moller GM, van Suylen RJ, van Spijk MP, Cloots RH, Hoet PH, Pennings HJ, Wouters EF.. Increased granzyme A expression in type II pneumocytes of patients with severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007 Mar 1;175(5):464-72. Epub 2006 Nov 30.

Metkar SS, Menaa C, Pardo J, Wang B, Wallich R, Freudenberg M, Kim S, Raja SM, Shi L, Simon MM, Froelich CJ.. Human and mouse granzyme A induce a proinflammatory cytokine response. Immunity. 2008 Nov 14;29(5):720-33. Epub 2008 Oct 23.

Baran K, Dunstone M, Chia J, Ciccone A, Browne KA, Clarke CJ, Lukoyanova N, Saibil H, Whisstock JC, Voskoboinik I, Trapani JA.. The molecular basis for perforin oligomerization and transmembrane pore assembly. Immunity. 2009 May;30(5):684-95. Epub 2009 May 14.

Froelich CJ, Pardo J, Simon MM.. Granule-associated serine proteases: granzymes might not just be killer proteases. Trends Immunol. 2009 Mar;30(3):117-23. Epub 2009 Feb 13. (REVIEW)

Hendel A, Hiebert PR, Boivin WA, Williams SJ, Granville DJ.. Granzymes in age-related cardiovascular and pulmonary diseases. Cell Death Differ. 2010 Apr;17(4):596-606. Epub 2010 Feb 5. (REVIEW)

Lieberman J.. Granzyme A activates another way to die. Immunol Rev. 2010 May;235(1):93-104. (REVIEW)

Praper T, Sonnen A, Viero G, Kladnik A, Froelich CJ, Anderluh G, Dalla Serra M, Gilbert RJ.. Human perforin employs different avenues to damage membranes. J Biol Chem. 2011 Jan 28;286(4):2946-55. Epub 2010 Oct 2.

Thiery J, Keefe D, Boulant S, Boucrot E, Walch M, Martinvalet D, Goping IS, Bleackley RC, Kirchhausen T, Lieberman J.. Perforin pores in the endosomal membrane trigger the release of endocytosed granzyme B into the cytosol of target cells. Nat Immunol. 2011 Jun 19;12(8):770-7. doi: 10.1038/ni.2050.

This article should be referenced as such:

Catalan E, Sanchez-Martinez D, Pardo J. GZMA (granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3)). Atlas Genet Cytogenet Oncol Haematol. 2012; 16(2):123-126.