

Table 1 Role of each member of the gasdermin family

Gasdermin	Expression in tumors	Related signaling pathways/ Cytokines	Relation to cancer	Related diseases	Ref.
GSDMA	Silenced in gastric cancer tissues and cell lines	Upregulated by TGF- β /LMO1 and TNF- α	Anti-oncogene	IBD, Iasthma, alopecia, and limited cutaneous systemic sclerosis	[1-6]
GSDMB	Expressed in rectal, colon, cervical, and pancreatic cancers and barely expressed in lung, liver, and breast cancers	1 Cleaved by caspase-1/3/4/6/7/8/9; 2 Participates In TGF- β -related airway remodeling; and 3 Upregulated by NF- κ B pathway	Oncogene	IBD, sepsis, and asthma	[2, 4, 7-11]
GSDMC	Upregulated in colorectal cancer and melanoma	1 Participates in ERK and JNK pathway-related MMP-1 expression; and 2 Upregulated by TGF- β -null	Oncogene	Uncertain	[12-16]
GSDMD	Expressed in gastric, esophageal,	1 Cleaved by caspase-1/4/5/8/11 and	Anti-oncogene	Inflammation-driven diseases	[17-23]

	pancreatic, and prostate cancers and melanoma	neutrophil elastase; Participates in IL-1 β and IL-18 secretion			
GSDME	Epigenetically inactivated by DNA methylation in breast, colorectal, and gastric cancers and most human cancer cell lines	1 Cleaved by caspase-3; Participates in caspase-3-mediated apoptotic	by Anti-oncogene	Hearing loss	[24-30]
DFNB59	Unknown	Participates in oxidative stress-induced peroxisome proliferation and pexophagy	Uncertain	Hearing loss	[31]

GSDMA: gasdermin A, TGF- β : transforming growth factor- β , LMO1: LIM domain only 1, TNF- α : tumor necrosis factor- α , GSDMB: gasdermin B, NF- κ B: nuclear factor- κ B, IBD: inflammatory bowel disease, GSDMC: gasdermin C, ERK: extracellular signal-regulated kinase, JNK: c-Jun N-terminal kinase, MMP-1: matrix metalloproteinase-1, GSDMD: gasdermin D, GSDME: gasdermin E, DFNB59: autosomal recessive deafness type 59 protein.

REFERENCES

- [1] Tanaka S, Fujii T, Aoki A, Komiyama H, Ezawa K, Sumiyama K, Sagai T and Shiroishi T. Members of a novel gene family, *Gsdm*, are expressed exclusively in the epithelium of the skin and gastrointestinal tract in a highly tissue-specific manner. *Genomics* 2007; 89: 618-629.
- [2] Yu J, Kang MJ, Kim BJ, Kwon JW, Song YH, Choi WA, Shin YJ and Hong SJ. Polymorphisms in *GSDMA* and *GSDMB* are associated with asthma susceptibility, atopy and BHR. *Pediatr Pulmonol* 2011; 46: 701-708.
- [3] Terao C, Kawaguchi T, Dieude P, Varga J, Kuwana M, Hudson M, Kawaguchi Y, Matucci-Cerinic M, Ohmura K, Riemekasten G, Kawasaki A, Airo P, Horita T, Oka A, Hachulla E, Yoshifuji H, Caramaschi P, Hunzelmann N, Baron M, Atsumi T, Hassoun P, Torii T, Takahashi M, Tabara Y, Shimizu M, Tochimoto A, Ayuzawa N, Yanagida H, Furukawa H, Tohma S, Hasegawa M, Fujimoto M, Ishikawa O, Yamamoto T, Goto D, Asano Y, Jinnin M, Endo H, Takahashi H, Takehara K, Sato S, Ihn H, Raychaudhuri S, Liao K, Gregersen P, Tsuchiya N, Ricciari V, Melchers I, Valentini G, Cauvet A, Martinez M, Mimori T, Matsuda F and Allanore Y. Transethnic meta-analysis identifies *GSDMA* and *PRDM1* as susceptibility genes to systemic sclerosis. *Ann Rheum Dis* 2017; 76: 1150-1158.
- [4] Soderman J, Berglind L and Almer S. Gene Expression-Genotype Analysis Implicates *GSDMA*, *GSDMB*, and *LRRC3C* as Contributors to Inflammatory Bowel Disease Susceptibility. *Biomed Res Int* 2015; 2015: 834805.
- [5] Li J, Zhou Y, Yang T, Wang N, Lian X and Yang L. *Gsdma3* is required for hair follicle differentiation in mice. *Biochem Biophys Res Commun* 2010; 403: 18-23.
- [6] Orning P, Lien E and Fitzgerald KA. Gasdermins and their role in immunity and inflammation. *J Exp Med* 2019; 216: 2453-2465.
- [7] Li L, Li Y and Bai Y. Role of *GSDMB* in Pyroptosis and Cancer. *Cancer Manag Res* 2020; 12: 3033-3043.
- [8] Das S, Miller M and Broide DH. Chromosome 17q21 Genes *ORMDL3* and

GSDMB in Asthma and Immune Diseases. *Adv Immunol* 2017; 135: 1-52.

[9] Li X, Christenson SA, Modena B, Li H, Busse WW, Castro M, Denlinger LC, Erzurum SC, Fahy JV, Gaston B, Hastie AT, Israel E, Jarjour NN, Levy BD, Moore WC, Woodruff PG, Kaminski N, Wenzel SE, Bleecker ER, Meyers DA and Program NSAR. Genetic analyses identify GSDMB associated with asthma severity, exacerbations, and antiviral pathways. *J Allergy Clin Immunol* 2021; 147: 894-909.

[10] Sarrió D, Molina-Crespo Á, Megias D, Mota A, Rojo-Sebastian A, García-Sanz P, Morales S, Abril S, Cano A, Peinado H and Moreno-Bueno G. Gasdermin-B promotes invasion and metastasis in breast cancer cells. *PLoS One* 2014; 9: e90099.

[11] Sarrió D, Molina-Crespo Á, Vicario R, Bernadó-Morales C, Martínez L, Rojo-Sebastián A, Serra-Musach J, Mota A, Martínez-Ramírez Á, Castilla M, González-Martin A, Pernas S, Cano A, Cortes J, Nuciforo PG, Peg V, Palacios J, Pujana M, Arribas J and Moreno-Bueno G. Gasdermin B expression predicts poor clinical outcome in HER2-positive breast cancer. *Oncotarget* 2016; 7: 56295-56308.

[12] Wei J, Xu Z, Chen X, Wang X, Zeng S, Qian L, Yang X, Ou C, Lin W, Gong Z and Yan Y. Overexpression of GSDMC is a prognostic factor for predicting a poor outcome in lung adenocarcinoma. *Mol Med Rep* 2020; 21: 360-370.

[13] Hinoi T, Shimomura M, Adachi T, Saito Y, Niitsu H, Kochi M, Sada H, Sotomaru Y, Ikenoue T, Shigeyasu K, Tanakaya K, Kitadai Y, Sentani K, Oue N, Yasui W and Ohdan H. Gasdermin C Is Upregulated by Inactivation of Transforming Growth Factor β Receptor Type II in the Presence of Mutated Apc, Promoting Colorectal Cancer Proliferation. *PLoS One* 2016; 11: e0166422.

[14] Hou J, Zhao R, Xia W, Chang CW, You Y, Hsu JM, Nie L, Chen Y, Wang YC, Liu C, Wang WJ, Wu Y, Ke B, Hsu JL, Huang K, Ye Z, Yang Y, Xia X, Li Y, Li CW, Shao B, Tainer JA and Hung MC. PD-L1-mediated gasdermin C expression switches apoptosis to pyroptosis in cancer cells and facilitates tumour necrosis. *Nat Cell Biol* 2020; 22: 1264-1275.

- [15] Kusumaningrum N, Lee DH, Yoon HS, Kim YK, Park CH and Chung JH. Gasdermin C is induced by ultraviolet light and contributes to MMP-1 expression via activation of ERK and JNK pathways. *J Dermatol Sci* 2018; 90: 180-189.
- [16] Kusumaningrum N, Lee DH, Yoon HS, Park CH and Chung JH. Ultraviolet light-induced gasdermin C expression is mediated via TRPV1/calcium/calcineurin/NFATc1 signaling. *Int J Mol Med* 2018; 42: 2859-2866.
- [17] Wan H, Hu L, Chen P, Wang X, Huang Z, Yang ZH, Zhong CQ and Han J. Gasdermin D is an executor of pyroptosis and required for interleukin-1 β secretion. *Cell Res* 2015; 25: 1285-1298.
- [18] Li L, Li Z and Wei Y. Gasdermin D (GSDMD) as a new target for the treatment of infection. *Medchemcomm* 2019; 10: 660-667.
- [19] Gao J, Wan B, Zhan P, Xu W, Lv T and Song Y. GSDMD is required for effector CD8(+) T cell responses to lung cancer cells. *Int Immunopharmacol* 2019; 74: 105713.
- [20] Liu F, Zhang X, Liu P, Bajrami B, Teng Y, Zhao L, Zhou S, Yu H, Zhou W, Silberstein LE, Cheng T, Han M, Xu Y and Luo HR. Gasdermin D Exerts Anti-inflammatory Effects by Promoting Neutrophil Death. *Cell Rep* 2018; 22: 2924-2936.
- [21] Monteleone M, Boucher D, Sollberger G, Ramnath D, Condon ND, von Pein JB, Broz P, Sweet MJ and Schroder K. Noncanonical inflammasome signaling elicits gasdermin D-dependent neutrophil extracellular traps. *Sci Immunol* 2018; 3: eaar6676.
- [22] Dick MS, Sborgi L, Meunier E, Hiller S and Broz P. The Gasdermin-D pore acts as a conduit for IL-1 β secretion in mice. *Eur J Immunol* 2018; 48: 584-592.
- [23] Evavold CL, Ruan J, Tan Y, Xia S, Wu H and Kagan JC. The Pore-Forming Protein Gasdermin D Regulates Interleukin-1 Secretion from Living Macrophages. *Immunity* 2018; 48: 35-44 e36.
- [24] De Schutter E, Croes L, Ibrahim J, Pauwels P, Op de Beeck K, Vandenabeele

P and Van Camp G. GSDME and its role in cancer: From behind the scenes to the front of the stage. *Int J Cancer* 2021; 148: 2872-2883.

[25]Jiang M, Qi L, Li L and Li Y. The caspase-3/GSDME signal pathway as a switch between apoptosis and pyroptosis in cancer. *Cell Death Discov* 2020; 6: 112.

[26]Yin B, Li D, Wang G, Han X and Sun X. GSDME mediates caspase-3-dependent pyroptosis in gastric cancer. *Biochem Biophys Res Commun* 2018; 495: 1418-1425.

[27]Ibrahim J, De Schutter E and Op de Beeck K. GSDME: A Potential Ally in Cancer Detection and Treatment. *Trends Cancer* 2021; 7: 392-394.

[28]Zhang Z, Zhang H, Li D, Zhou X, Qin Q and Zhang Q. Caspase-3-mediated GSDME induced Pyroptosis in breast cancer cells through the ROS/JNK signalling pathway. *J Cell Mol Med* 2021; 25: 8159-8168.

[29]Zhang Z, Zhao S, Yang H, Chen Y, Feng H, An M and Chen B. Prognostic and Immunological Role of Gasdermin E in Pan-Cancer Analysis. *Front Oncol* 2021; 11: 706266.

[30]Park HJ, Cho HJ, Baek JI, Ben-Yosef T, Kwon TJ, Griffith AJ and Kim UK. Evidence for a founder mutation causing DFNA5 hearing loss in East Asians. *J Hum Genet* 2010; 55: 59-62.

[31]Collin RW, Kalay E, Oostrik J, Caylan R, Wollnik B, Arslan S, den Hollander AI, Birinci Y, Lichtner P, Strom TM, Toraman B, Hoefsloot LH, Cremers CW, Brunner HG, Cremers FP, Karaguzel A and Kremer H. Involvement of DFNB59 mutations in autosomal recessive nonsyndromic hearing impairment. *Hum Mutat* 2007; 28: 718-723.