GSDM家族蛋白的结构和功能分析

The structure and function analyze of GSDM family

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ARTICLE

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Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death

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ARTICLE

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Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling

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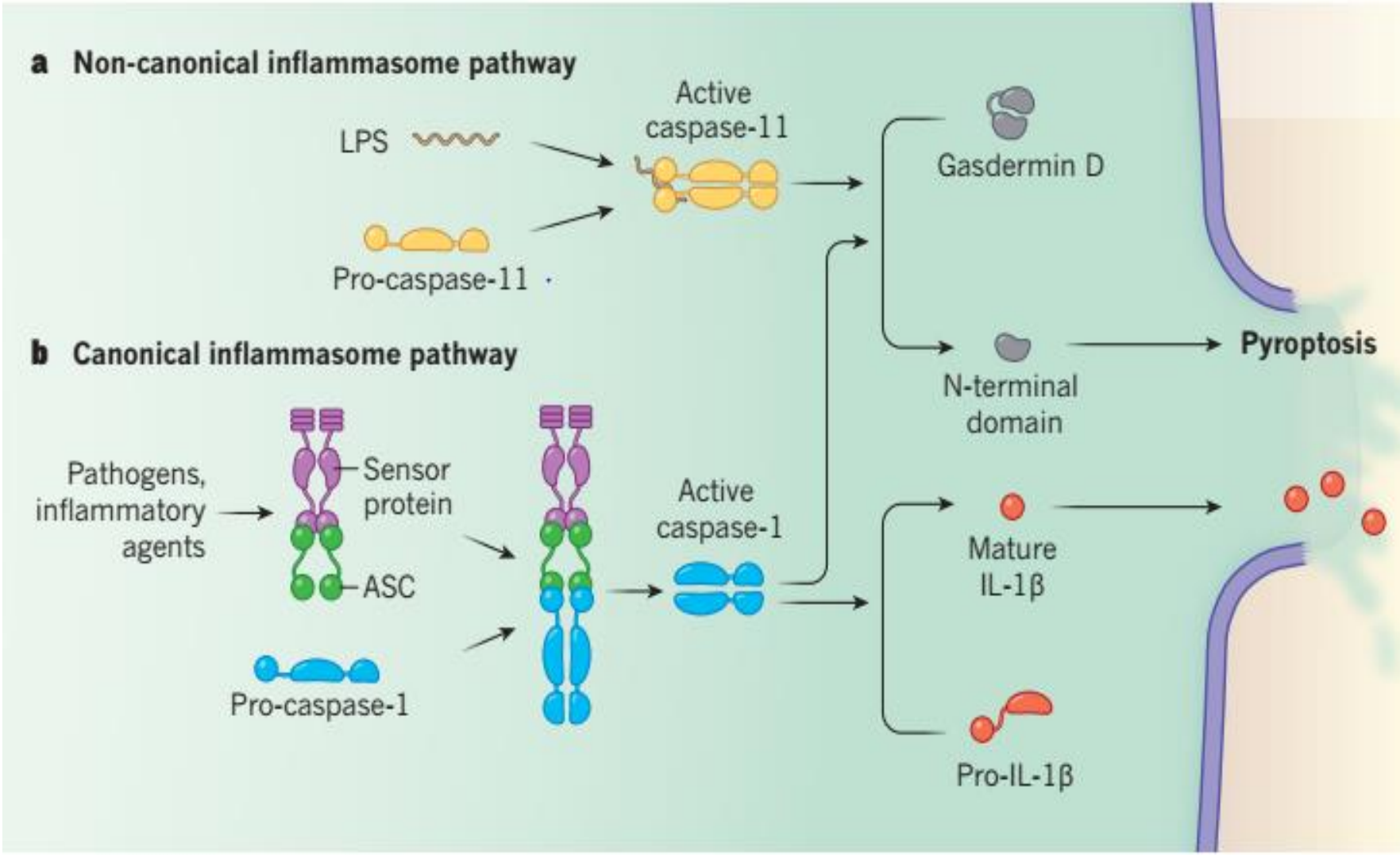
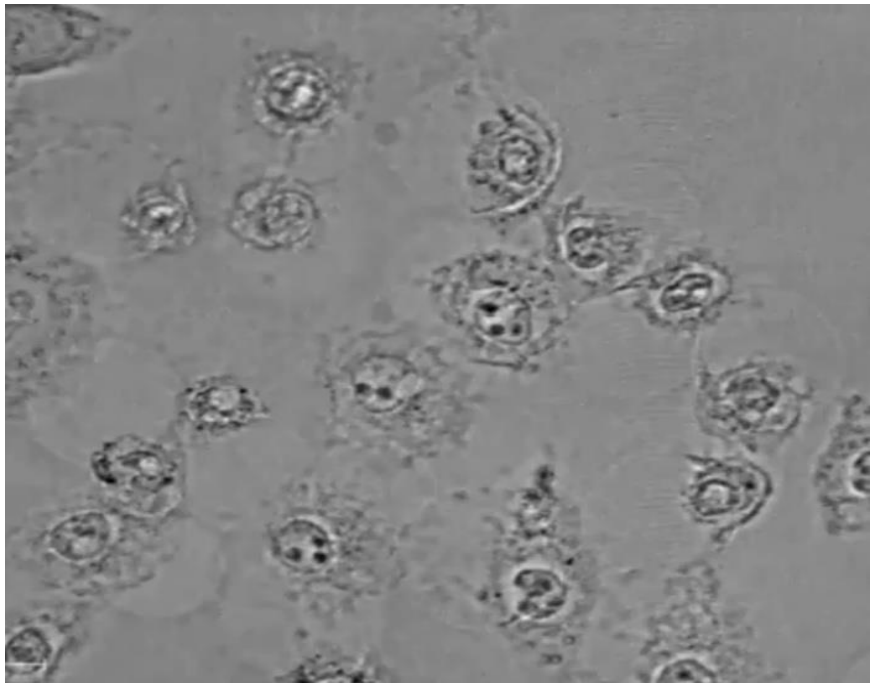
炎性反应简介


a Non-canonical inflammasome pathway
LPS
Active caspase-11
Pro-caspase-11
Gasdermin D
N-terminal domain
Pyroptosis
b Canonical inflammasome pathway
Pathogens, inflammatory agents
Sensor protein
ASC
Pro-caspase-1
Active caspase-1
Mature IL-1β
Pro-IL-1β

细胞焦亡（pyroptosis）简介

- 细胞焦亡（pyroptosis）是近年来发现并证实的一种新的细胞程序性死亡方式。

- 细胞焦亡过程中，细胞膜上会有小孔形成，细胞溶胀、质膜破裂，然后导致细胞内容物大量外泄引发炎症反应。细胞焦亡与细胞凋亡的形态特征、发生机制等有明显不同。



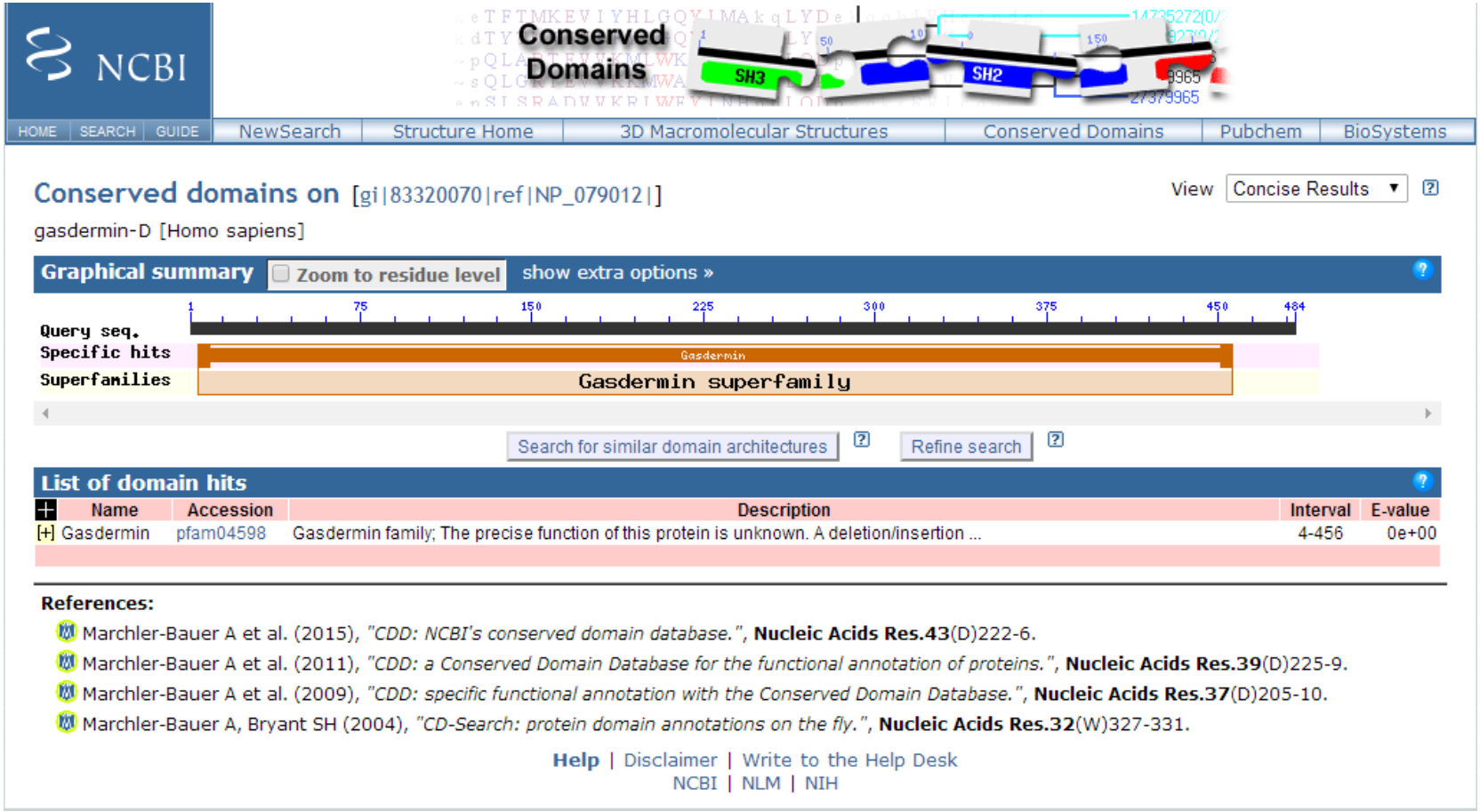
GSDMD蛋白简介

- *GSDMD*定位于人的第八号染色体上，编码484个氨基酸，含有14个外显子。GSDMD蛋白是经典和非经典炎性反应途径的下游非常重要的靶蛋白，它被caspase切割后会引起细胞焦亡。

- 实验分析表明，在293T细胞中分别过表达GSDMD蛋白的N端，C端以及全长的蛋白，GSDMD的N端会引起大量的细胞死亡并表现出明显的细胞焦亡的特征。

- GSDMD　P57764
- http://www.uniprot.org/uniprot/P57764

利用CD-search对GSDMD蛋白进行分析



https://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi

GSDM家族蛋白简介

- gasdermin family

- http://www.uniprot.org/uniprot/?query=family%3A"gasdermin+family"+AND+organism%3A"Human+%5B9606%5D"&sort=score

Suggest adding column(s): Protein families

Entry	Entry name		Protein names	Gene names	Organism	Length
P57764	GSDMD_HUMAN		**Gasdermin-D**	**GSDMD** DFNA5L, GSDMDC1, FKSG10	Homo sapiens (Human)	484
O60443	DFNA5_HUMAN		**Non-syndromic hearing impairment pr...**	**DFNA5** ICERE1	Homo sapiens (Human)	496
Q8TAX9	GSDMB_HUMAN		**Gasdermin-B**	**GSDMB** GSDML, PP4052, PRO2521	Homo sapiens (Human)	411
Q9BYG8	GSDMC_HUMAN		**Gasdermin-C**	**GSDMC** MLZE	Homo sapiens (Human)	508
Q96QA5	GSDMA_HUMAN		**Gasdermin-A**	**GSDMA** GSDM, GSDM1, FKSG9	Homo sapiens (Human)	445
Q0ZLH3	PJVK_HUMAN		**Pejvakin**	**DFNB59** PJVK	Homo sapiens (Human)	352

1 to **6** of **6** Show 25

GSDM家族蛋白简介

- GSDM（Gasdermin domain containin）家族蛋白是一类含有Gasdermin结构域的蛋白家族，包括GSDMA（Gasdermin-A）、GSDMB （ Gasdermin-B ） 、 GSDMC （ Gasdermin-C ） 、GSDMD（Gasdermin-D）、DFNA5（Non-syndromic hearing impairment protein）、DFNB59（Pejvakin）六种蛋白，GSDM蛋白家族大约有45%的序列同源性。

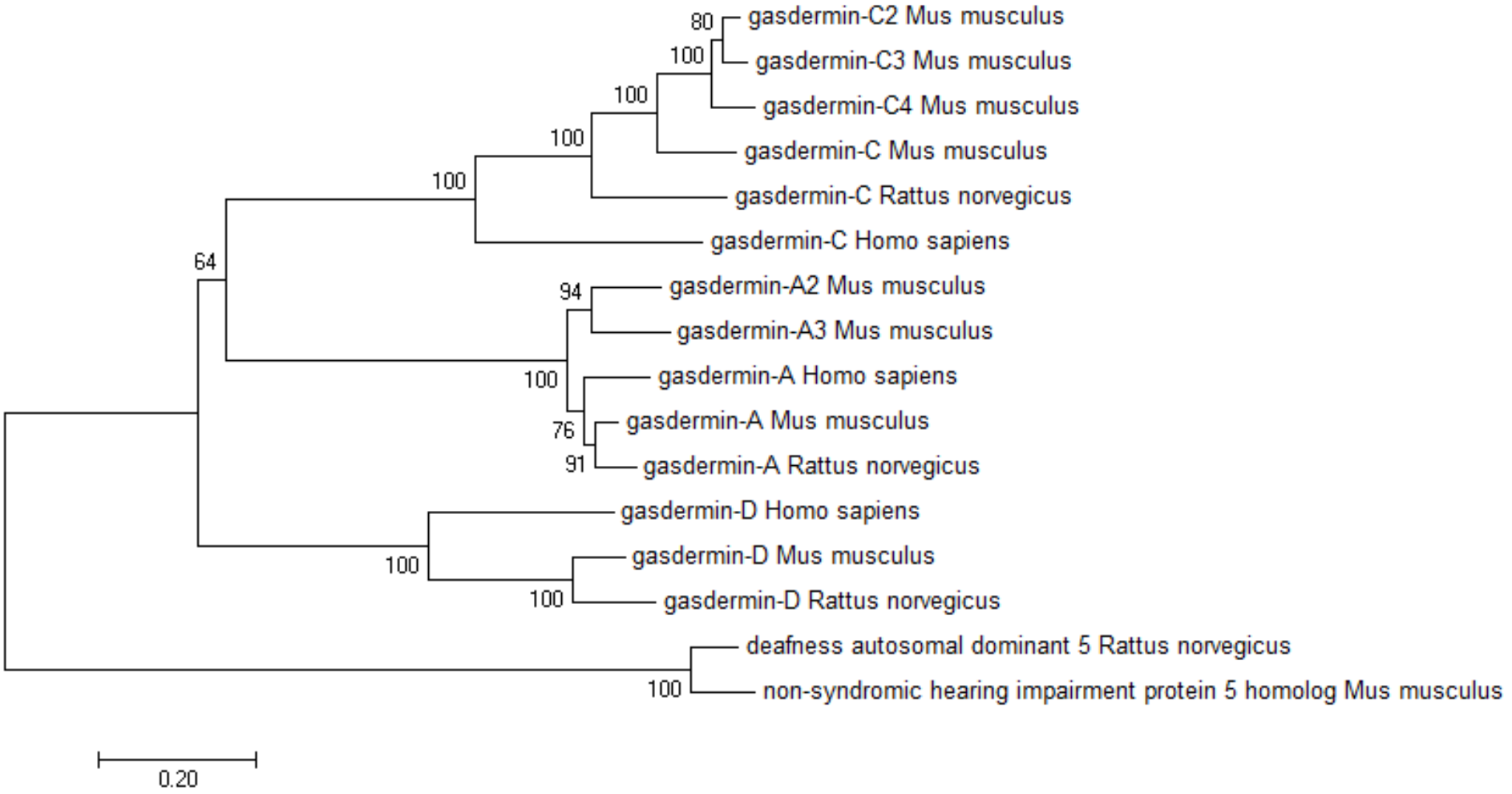
- Gasdermin结构域可以分为两部分，gasdermin-N 和 gasdermin -C 结构域，目前认为GSDM家族蛋白具有相似的自抑制机制，当受到外来信号刺激时可以释放出具有活性的N端结构域。

Protein names	Gene names	表达及功能	定位及编码
Gasdermin-D	***GSDMD***	作用于经典和非经典炎性反应途径的下游，引起细胞焦亡	人8号染色体，编码484个氨基酸，14个外显子
Non-syndromic hearing impairment protein	***DFNA5***	在多种肿瘤中都发现了具有重要作用，可能是一种抑癌基因	人7号染色体，编码496个氨基酸，11个外显子
Gasdermin-B	***GSDMB***	在乳腺、软骨和大肠肿瘤，正常肝脏、脾脏、皮肤和肌肉有较高表达	人17号染色体，9个外显子，8个内含子，存在多种剪接形式的转录本
Gasdermin-C	***GSDMC***	多表达于人的气管及脾脏中，可能是肿瘤抑制因子	人8号染色体上，含有12个外显子
Gasdermin-A	***GSDMA***	主要在胃肠道细胞中表达	人17号染色体，8个外显子，编码445个氨基酸
Pejvakin	***DFNB59***	在检测的人的组织，如大脑、眼、肾脏、肝脏、肺、心脏等组织中都有表达，主要作用于听觉通路的神经元中	人2号染色体，含有7个外显子，编码352个氨基酸

建树分析—直系同源序列

	Description	Max score	Total score	Query cover	E value	Ident	Accession
☑	gasdermin-D [Homo sapiens]	979	979	100%	0.0	100%	NP_079012.3
☑	gasdermin-D [Mus musculus]	489	489	99%	2e-173	58%	NP_081236.1
☑	gasdermin-D [Rattus norvegicus]	481	481	99%	7e-171	55%	NP_001124025.1
☑	gasdermin-A [Rattus norvegicus]	208	208	98%	7e-65	34%	NP_001101767.1
☑	gasdermin-A [Mus musculus]	197	197	98%	1e-60	33%	NP_067322.1
☐	gasdermin domain containing protein RGD1359449 [Rattus norvegicus]	197	197	84%	2e-60	33%	NP_001014106.1
☑	gasdermin-A [Homo sapiens]	186	186	98%	1e-56	32%	NP_835465.2
☑	gasdermin-A3 [Mus musculus]	187	187	99%	1e-56	33%	NP_001007462.1
☑	gasdermin-A2 [Mus musculus]	184	184	99%	6e-56	32%	NP_084003.2
☑	gasdermin-C [Homo sapiens]	178	178	99%	5e-53	30%	NP_113603.1
☑	gasdermin-C [Rattus norvegicus]	148	148	98%	2e-42	30%	NP_001127967.1
☑	gasdermin-C2 [Mus musculus]	143	143	99%	2e-40	30%	NP_808580.2
☑	gasdermin-C3 [Mus musculus]	139	139	99%	7e-39	30%	NP_899017.2
☑	gasdermin-C [Mus musculus]	132	132	99%	1e-36	27%	NP_113555.1
☑	gasdermin-C4 [Mus musculus]	125	125	99%	5e-34	28%	NP_083268.1
☑	non-syndromic hearing impairment protein 5 homolog [Mus musculus]	57.8	57.8	45%	8e-12	26%	NP_061239.1
☑	deafness, autosomal dominant 5 [Rattus norvegicus]	47.4	47.4	36%	2e-08	27%	NP_001178678.1

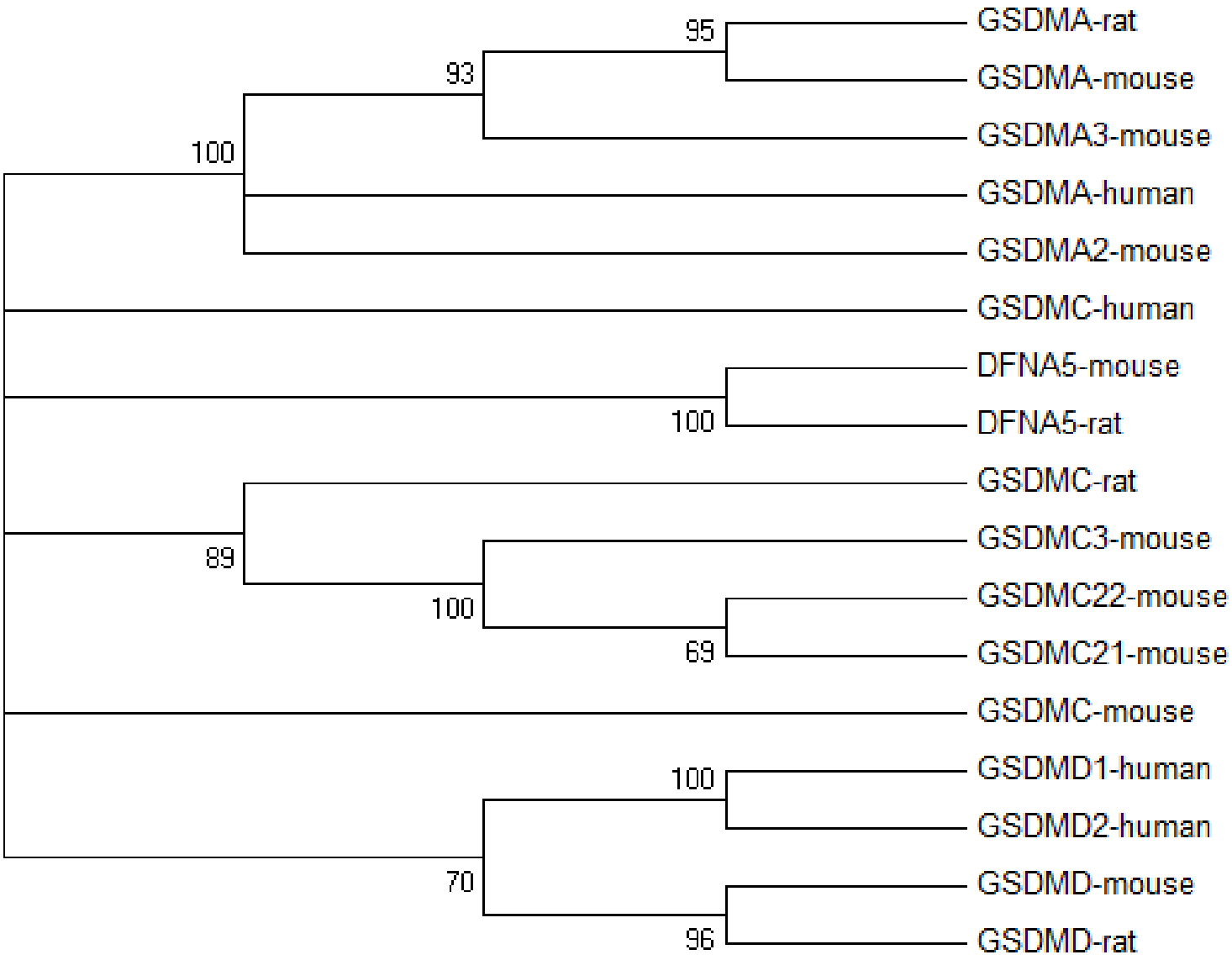
建树分析—直系同源序列


80
100
100
100
100
64
94
100
76
91
100
100
gasdermin-C2 Mus musculus
gasdermin-C3 Mus musculus
gasdermin-C4 Mus musculus
gasdermin-C Mus musculus
gasdermin-C Rattus norvegicus
gasdermin-C Homo sapiens
gasdermin-A2 Mus musculus
gasdermin-A3 Mus musculus
gasdermin-A Homo sapiens
gasdermin-A Mus musculus
gasdermin-A Rattus norvegicus
gasdermin-D Homo sapiens
gasdermin-D Mus musculus
gasdermin-D Rattus norvegicus
deafness autosomal dominant 5 Rattus norvegicus
non-syndromic hearing impairment protein 5 homolog Mus musculus
0.20

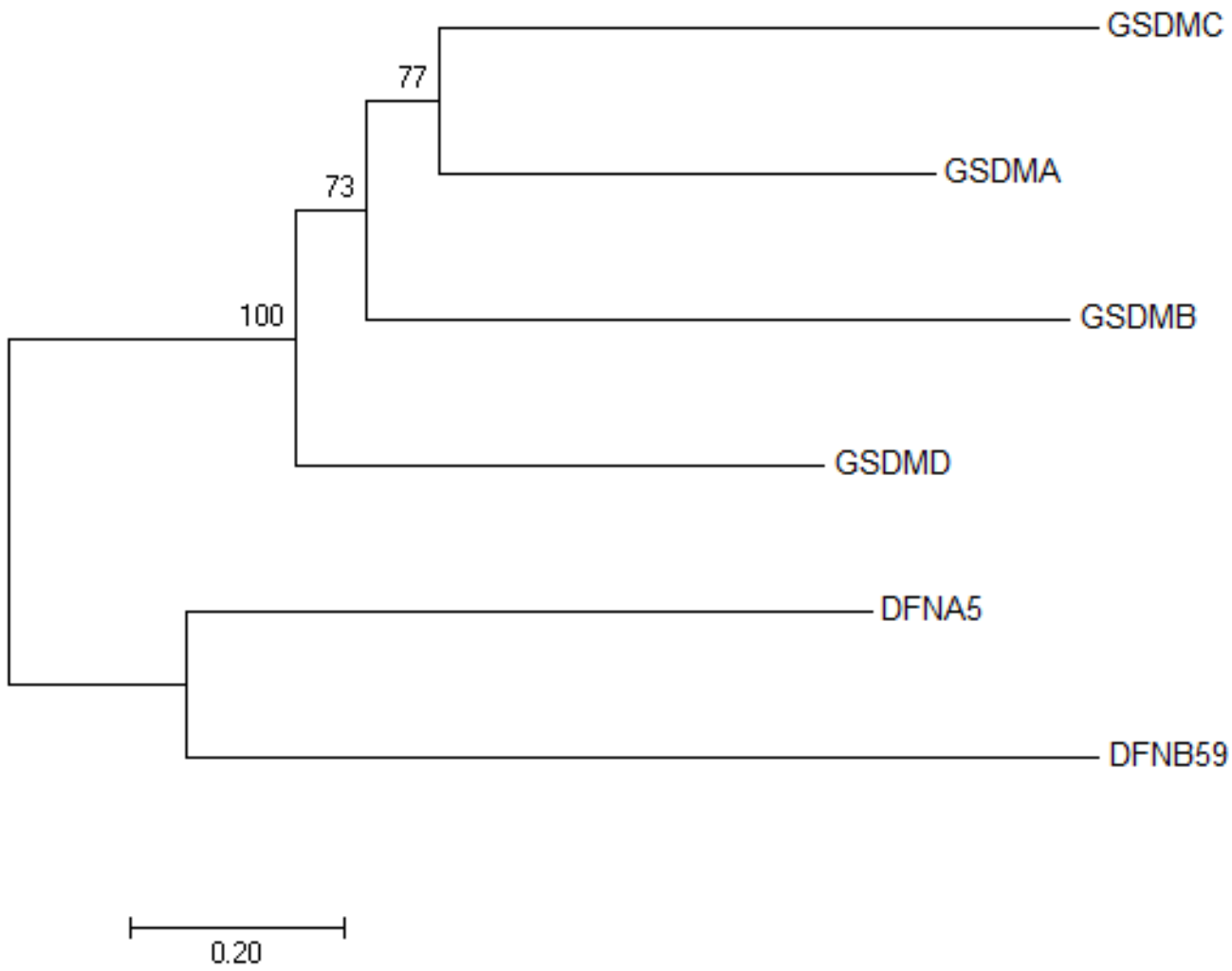
建树分析—直系同源序列

	Description	Max score	Total score	Query cover	E value	Ident	Accession
☑	Homo sapiens gasdermin D (GSDMD), transcript variant 1, mRNA	813	813	100%	0.0	85%	NM_024736.6
☑	Homo sapiens gasdermin D (GSDMD), transcript variant 2, mRNA	812	812	100%	0.0	85%	NM_001166237.1
☑	Mus musculus gasdermin D (Gsdmd), mRNA	407	407	95%	1e-139	51%	NM_026960.4
☑	Rattus norvegicus gasdermin D (Gsdmd), mRNA	394	394	96%	8e-135	48%	NM_001130553.1
☑	Rattus norvegicus gasdermin A (Gsdma), mRNA	153	153	96%	2e-42	28%	NM_001108297.1
☑	Mus musculus gasdermin A (Gsdma), mRNA	147	147	45%	2e-40	38%	NM_021347.4
☐	Rattus norvegicus gasdermin domain containing protein RGD1359449 (RGD1359449), mRNA	145	188	60%	2e-40	35%	NM_001014084.1
☐	Mus musculus gasdermin C-like, pseudogene (Gsdmcl-ps), non-coding RNA	142	142	81%	3e-39	29%	NR_029414.1
☑	Mus musculus gasdermin A3 (Gsdma3), mRNA	140	140	45%	5e-39	38%	NM_001007461.1
☐	Mus musculus gasdermin C-like 2 (Gsdmcl2), non-coding RNA	133	133	46%	2e-37	35%	NR_108053.1
☑	Homo sapiens gasdermin A (GSDMA), mRNA	137	137	49%	3e-37	35%	NM_178171.4
☑	Mus musculus gasdermin A2 (Gsdma2), mRNA	132	132	45%	5e-36	35%	NM_029727.2
☑	Homo sapiens gasdermin C (GSDMC), mRNA	105	105	82%	2e-26	26%	NM_031415.2
☐	Mus musculus gasdermin C-like 1 (Gsdmcl1), non-coding RNA	97.4	97.4	32%	9e-25	35%	NR_108051.1
☑	Rattus norvegicus gasdermin C (Gsdmc), mRNA	64.3	64.3	62%	1e-13	25%	NM_001134495.1
☑	Mus musculus deafness, autosomal dominant 5 (human) (Dfna5), mRNA	57.4	57.4	45%	2e-11	26%	NM_018769.3
☑	Mus musculus gasdermin C2 (Gsdmc2), transcript variant 2, mRNA	55.8	55.8	50%	6e-11	27%	NM_177912.4
☑	Mus musculus gasdermin C2 (Gsdmc2), transcript variant 1, mRNA	55.8	55.8	50%	6e-11	27%	NM_001168274.1
☑	Mus musculus gasdermin C3 (Gsdmc3), mRNA	50.4	50.4	50%	3e-09	26%	NM_183194.3
☑	Mus musculus gasdermin C (Gsdmc), mRNA	49.7	49.7	49%	5e-09	25%	NM_031378.3

建树分析—直系同源序列


95
93
100
100
89
100
69
100
70
96
GSDMA-rat
GSDMA-mouse
GSDMA3-mouse
GSDMA-human
GSDMA2-mouse
GSDMC-human
DFNA5-mouse
DFNA5-rat
GSDMC-rat
GSDMC3-mouse
GSDMC22-mouse
GSDMC21-mouse
GSDMC-mouse
GSDMD1-human
GSDMD2-human
GSDMD-mouse
GSDMD-rat

建树分析—旁系同源序列（人源）



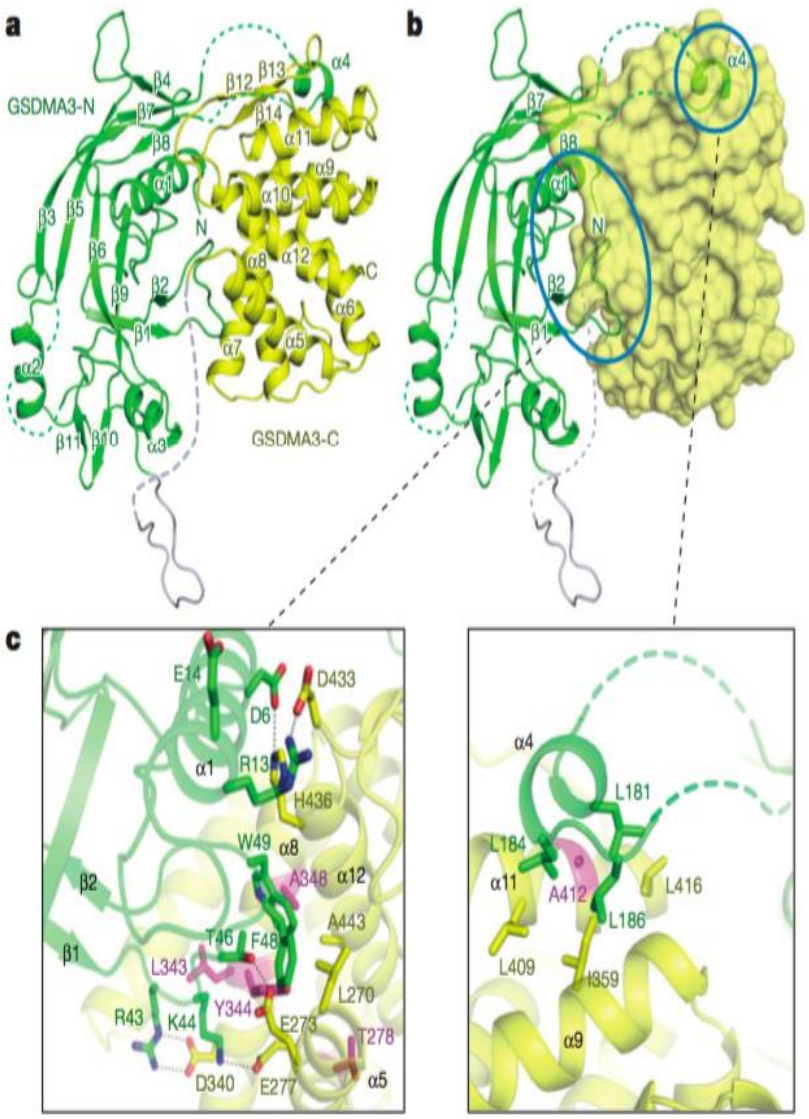
GSDM family (Uniprot)序列比对

Conserved in N terminal

GSDM family (Uniprot)序列比对

Un-conservative in C terminal

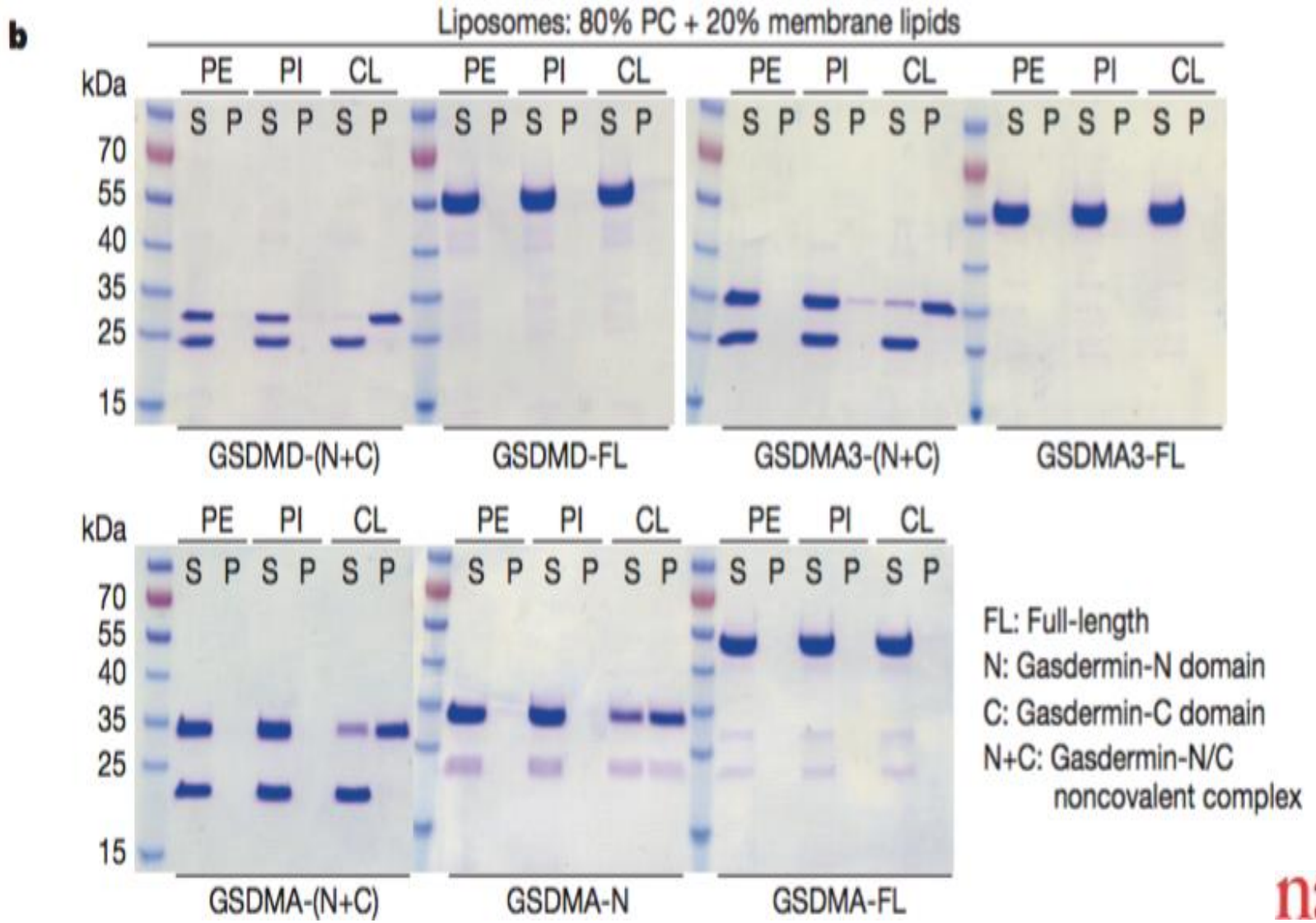
GSDMA3的晶体结构



nature

J Ding *et al. Nature* 1–6 (2016) doi:10.1038/nature18590

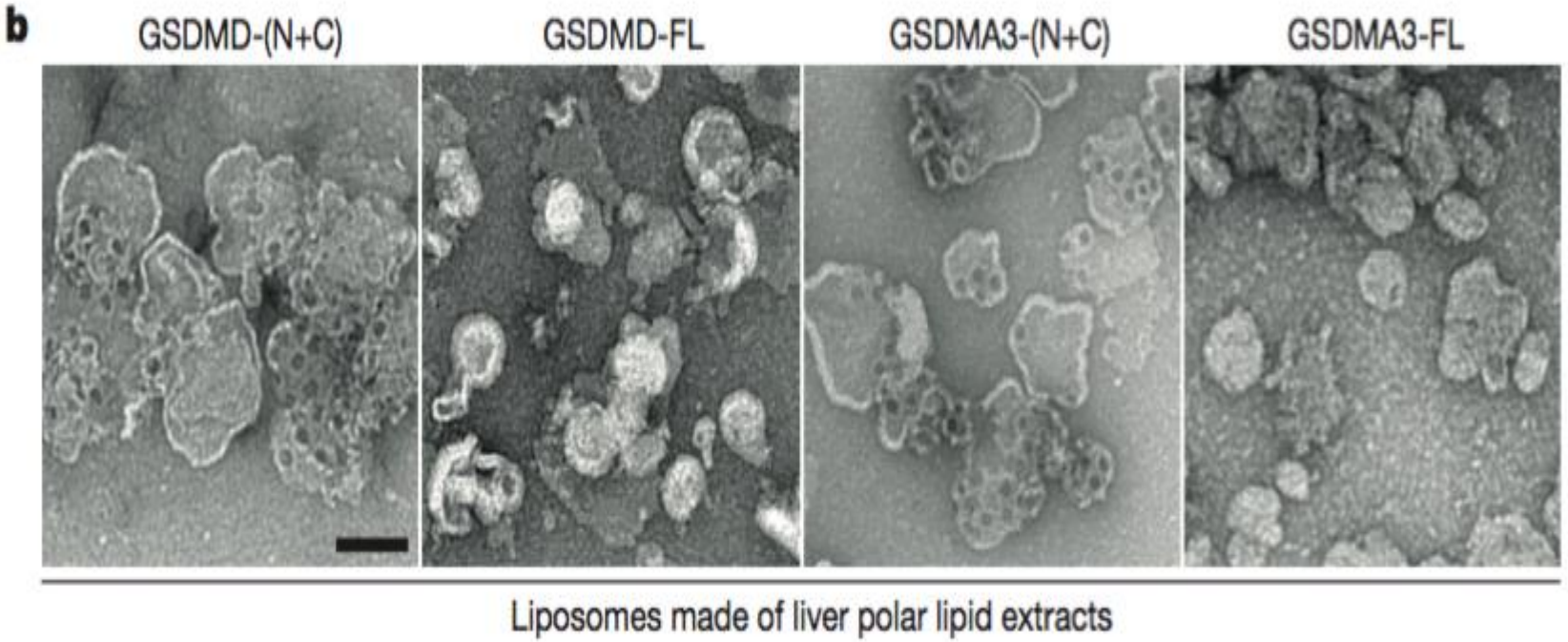
Gasdermin N端能够与质膜结合



nature

J Ding *et al. Nature* 1–6 (2016) doi:10.1038/nature18590

Gasdermin N 端能够诱导质膜破裂



nature

J Ding *et al. Nature* 1–6 (2016) doi:10.1038/nature18590

Summary :

1.GSDMD
- NCBI: CD search分析 → Gasdermin结构域
- Uniprot：GSDM家族蛋白
  - GSDMA
  - GSDMB
  - GSDMC
  - GSDMD
  - DFNA5
  - DFNB59

2.GSDMD
- BlastP
- tBlastN

→ Human、rat、mouse中的同源序列 → 序列比对 → 建树分析
- 直系同源
- 旁系同源

3.序列比对结果 → GSDM家族蛋白N端保守 → GSDM家族其他蛋白是否具有相似功能？ → 实验验证

Reference :

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8.Busch-Nentwich, E., et al., *The deafness gene dfna5 is crucial for ugdh expression and HA production in the developing ear in zebrafish.* Development, 2004. **131**(4): p. 943-51

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Thanks !