The potential anti-influenza A virus effects of hGBP1

hGBP1抗A型流感病毒的可能作用

G05

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Background

hGBP1——human Guanylate-Binding Protein 1

21. The interferon-induced 67-kDa guanylate-binding protein (**hGBP1**) is a GTPase that converts GTP to GMP.

Schwemmle M, Staeheli P.

J Biol Chem. 1994 Apr 15;269(15):11299-305.

PMID: 7512561 [PubMed - indexed for MEDLINE]

Related citations

在Swiss-Prot的登录号为P32455 （GBP1_HUMAN）

Sequence length	592AA
Protein existence	Evidence at protein level
Function	Binds GTP, GDP and GMP
Induction	By IFNG/IFN-gamma during macrophage activation
Sequence similarities	Belongs to the GBP family.
Biological process	interferon-gamma-mediated signaling pathway
Molecular function	GTP binding GTPase activity

二级结构

PDB数据库中的结构

Query Parameters: Query Details | Save Query to MyPDB

Text Search for: hgbp1

Query Refinements: *Select an item or pie chart* Hide

Organism
- Homo sapiens only (6)

Taxonomy
- Eukaryota only (6)

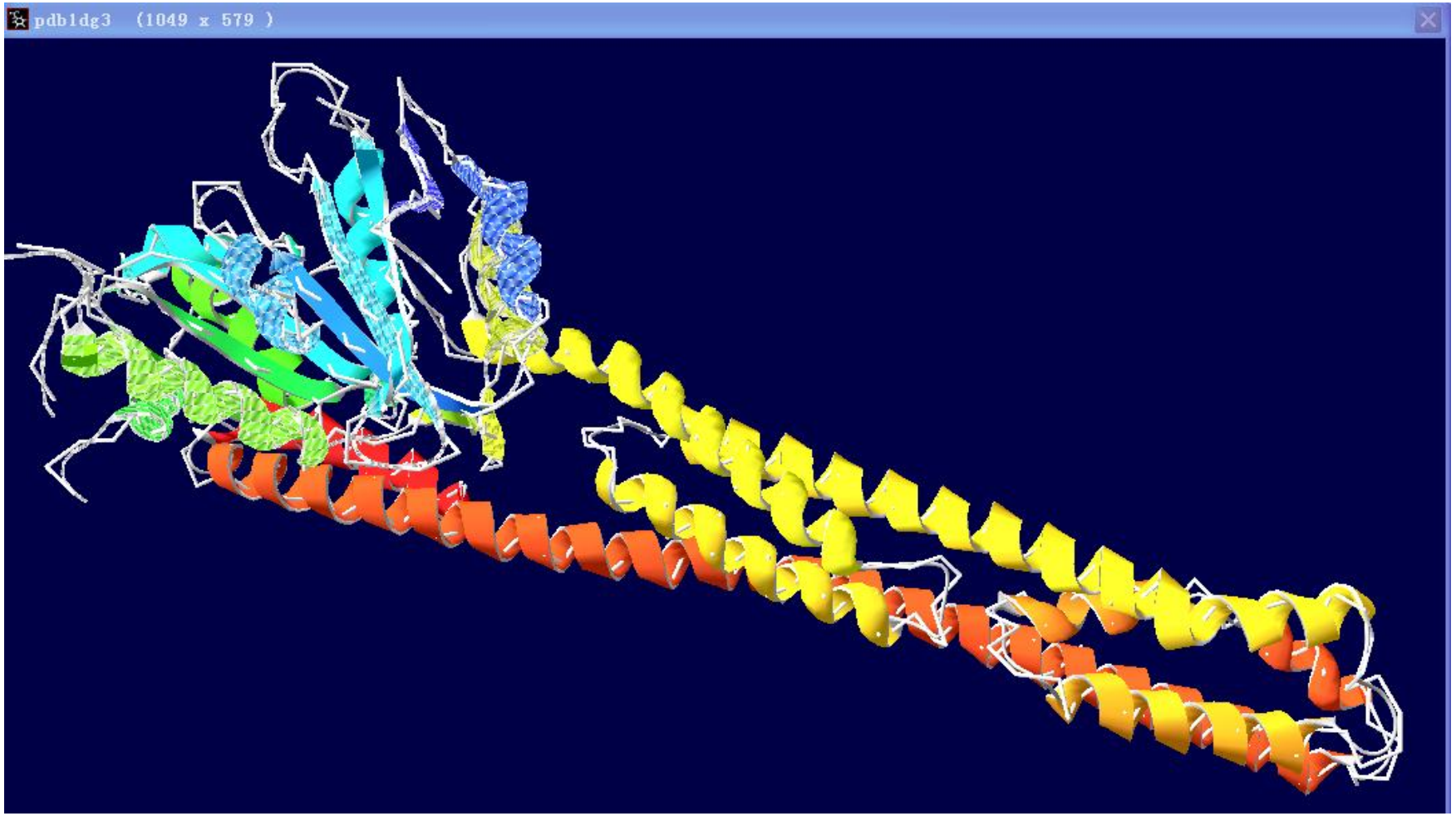
Experimental Method
- X-ray (6)

X-ray Resolution
- 1.5 - 2.0 Å (2)
- 2.0 - 2.5 Å (1)
- 2.5 - 3.0 Å (2)
- 3.0 and more Å (1)
- more choices...

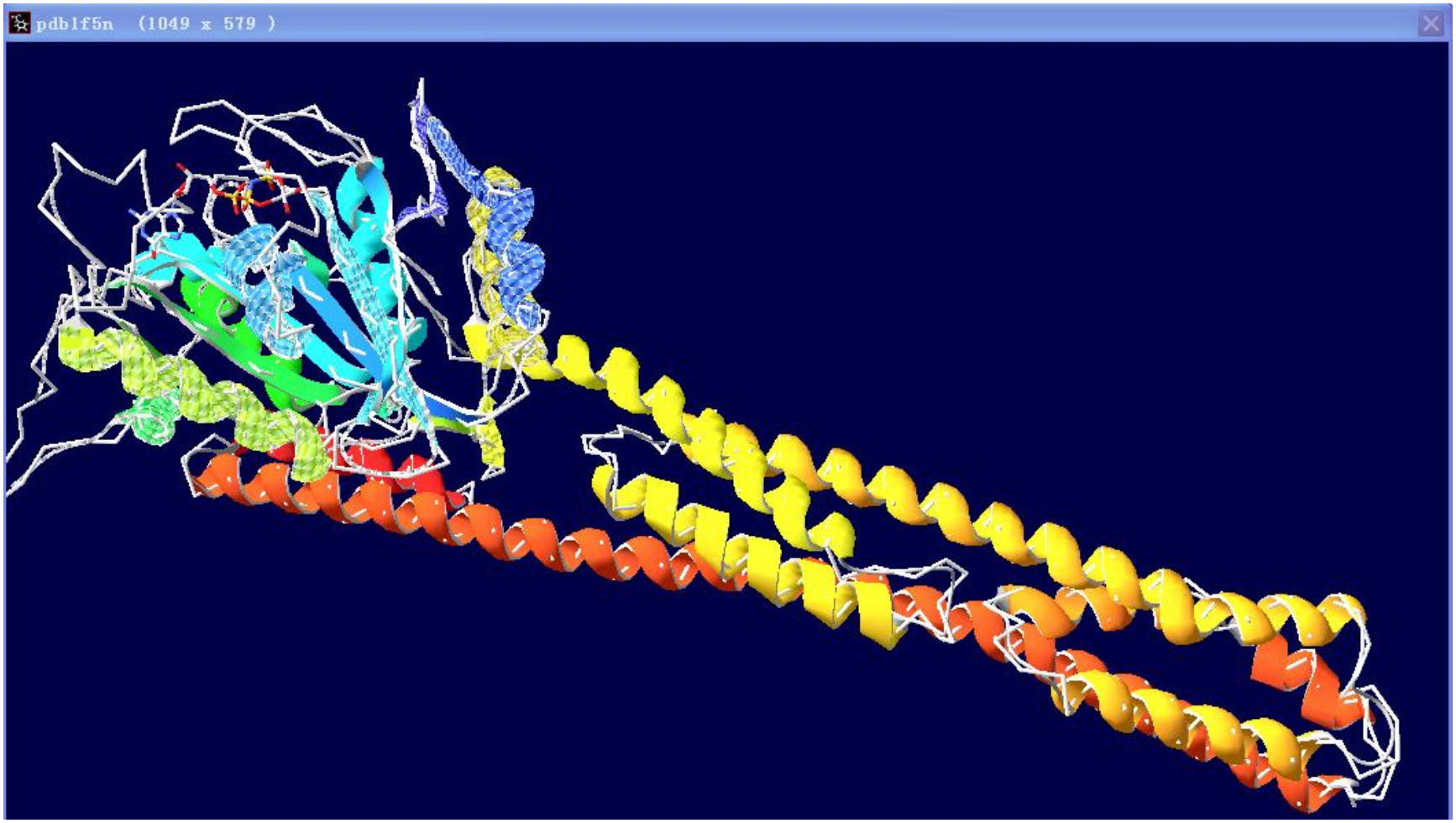
Release Date
- 2000 - 2005 (2)
- 2005 - 2010 (4)
- more choices...

Polymer Type
- Protein (6)

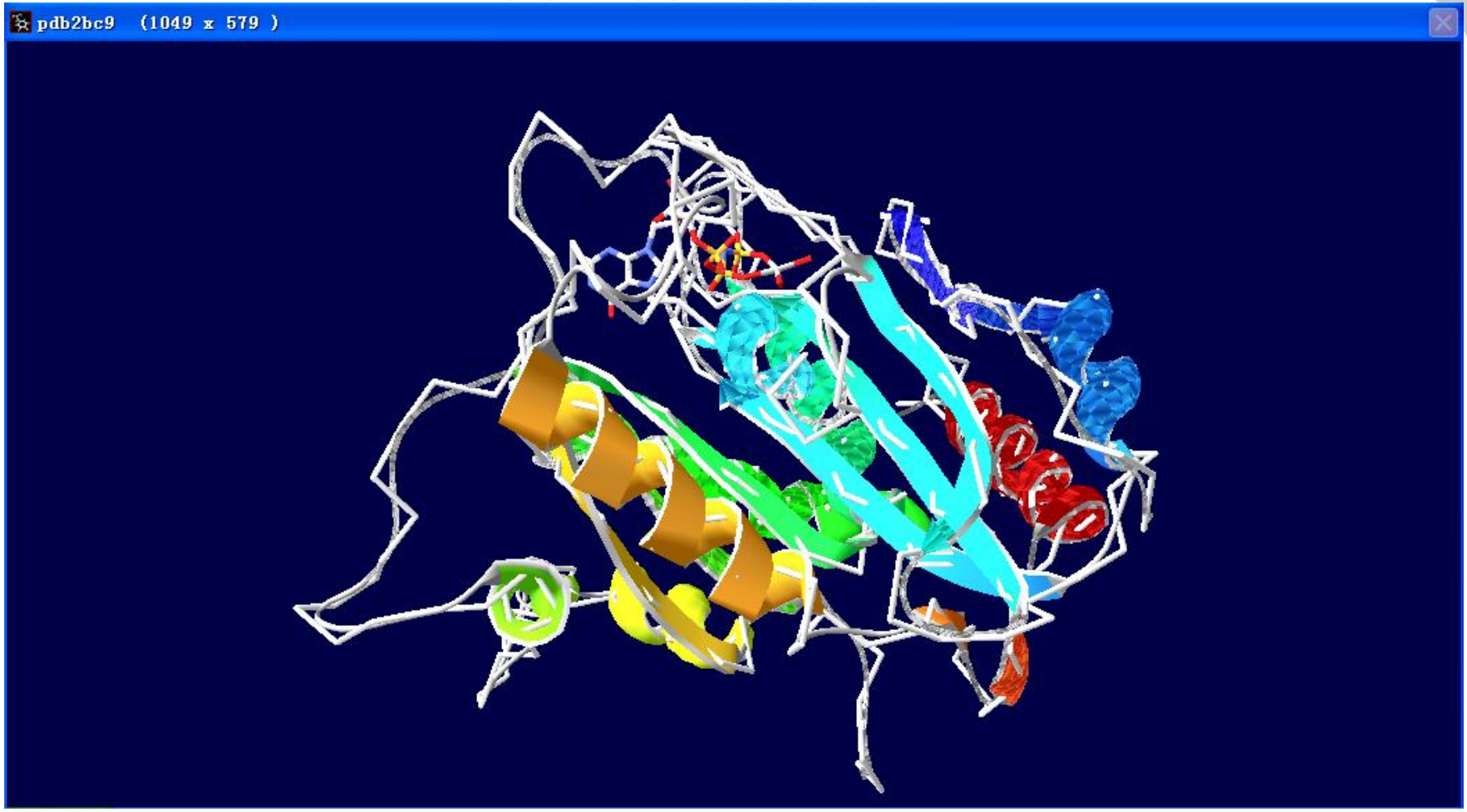
SCOP Classification
- Alpha and beta proteins (a/b) (2)
- All alpha proteins (2)



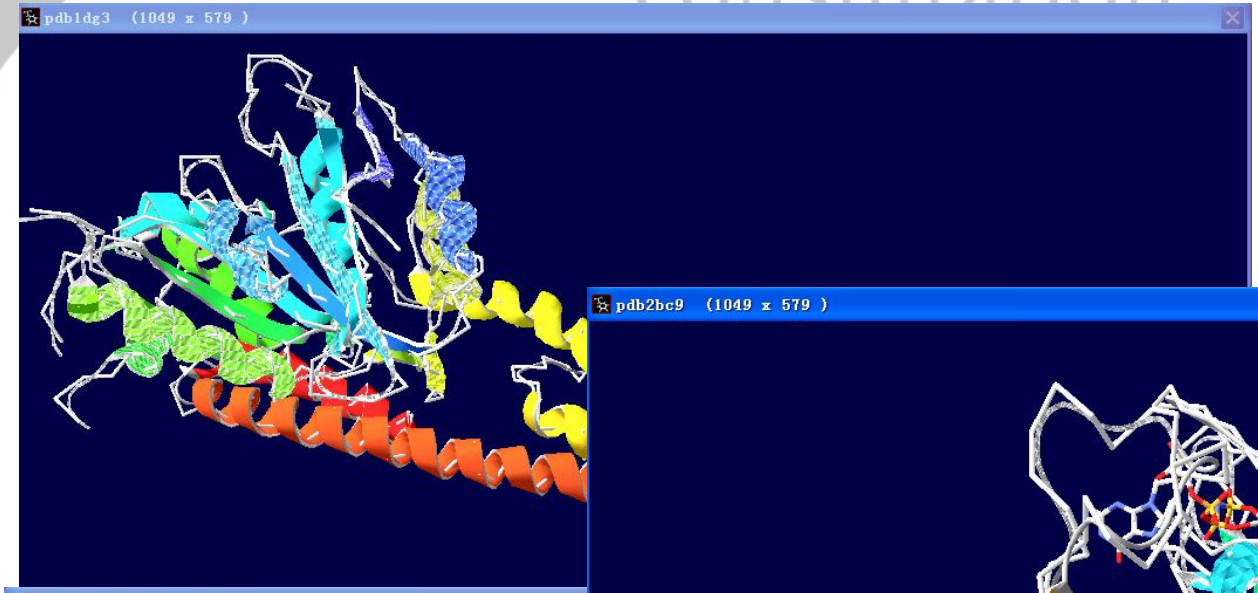
1DG3：STRUCTURE OF HUMAN GUANYLATE BINDING PROTEIN-1 IN NUCLEOTIDE FREE FORM



1F5N：HUMAN GUANYLATE BINDING PROTEIN-1 IN COMPLEX WITH THE GTP ANALOGUE, GMPPNP



2BC9： Crystal-structure of the N-terminal large GTPase Domain of human Guanylate Binding protein 1 (hGBP1) in complex with non-hydrolysable GTP analogue GppNHp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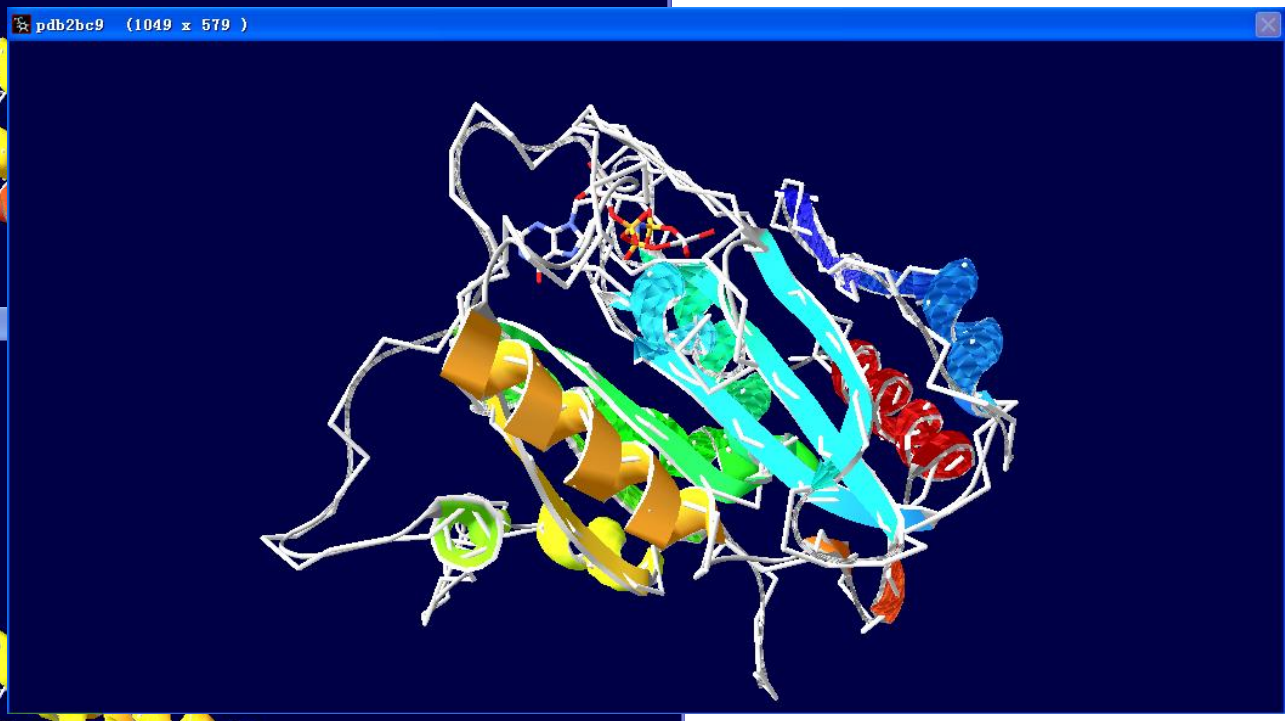
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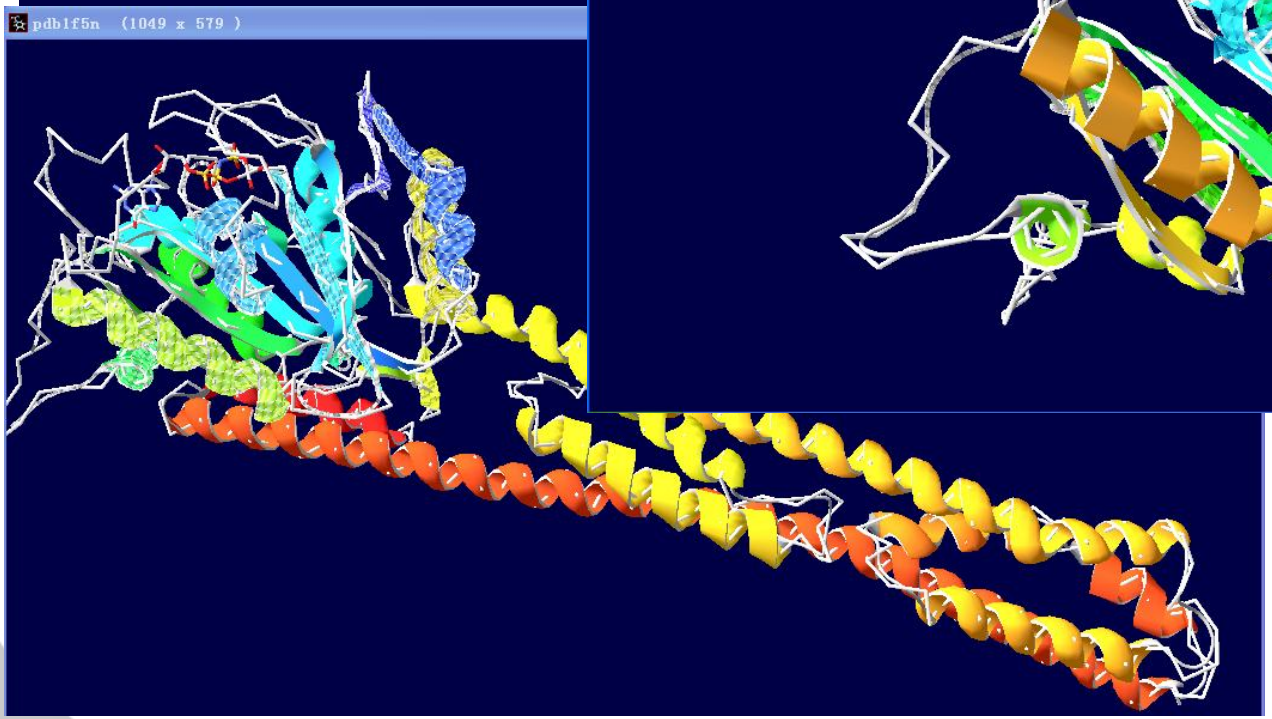
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The Guanylate-Binding Proteins: Emerging Insights into the Biochemical Properties and Functions of This Family of Large Interferon-Induced Guanosine Triphosphatase

Deborah J. Vestal and Jonathan A. Jeyaratnam

Antiviral activities. hGBP-1 has modest antiviral activity against the negative strand RNA Rhabdovirus, vesicular stomatitis virus, and the positive strand RNA Picornovirus and encephalomyocarditis virus in cultured cells (Anderson and others 1999). The putative murine ortholog of hGBP-1, mGBP-2, also shows modest activity against those same viruses (Carter and others 2005). Consistent with an antiviral activity for hGBP-1, it was identified as one of the ISGs whose RNA levels are repressed in Huh7 cells by the hepatitic C virus (HCV) replicon (Itsui and others 2006). Forced expression of hGBP-1 in Huh7 cells containing the HCV replicon inhibited replicon replication by 40% (Itsui and others 2006). hGBP-1 was shown to interact with HCV NS5B when co-transfected into HEK-293T cells (Itsui and others 2009). This interaction inhibited hGBP-1's GTPase activity and is proposed to inhibit the antiviral activity of hGBP-1 (Table 3). How expression of hGBP-1 is repressed by HCV is still unknown.

NS1：Non-structural protein 1

	Entry	Entry name	Status	Protein names	Gene names	Organism	Length
☐	P03495	NS1_I72A2	★	Non-structural protein 1	NS	Influenza A virus (strain A/Udorn/307/1972 H3N2)	237
☐	P03496	NS1_I34A1	★	Non-structural protein 1	NS	Influenza A virus (strain A/Puerto Rico/8/1934 H1N1)	230
☐	P03500	NS1_I34A0	★	Non-structural protein 1	NS	Influenza A virus (strain A/Fowl plague virus/Rostock/8/1934 H7N1)	230
☐	P69270	NS1_I76A2	★	Non-structural protein 1	NS	Influenza A virus (strain A/Duck/Alberta/60/1976 H12N5)	230
☐	Q82506	NS1_I33A0	★	Non-structural protein 1	NS	Influenza A virus (strain A/Wilson-Smith/1933 H1N1) (Influenza A virus (strain A/WS/1933 H1N1))	230
☐	O56264	NS1_I97A1	★	Non-structural protein 1	NS	Influenza A virus (strain A/Hong Kong/156/1997 H5N1 genotype Gs/Gd)	230
☐	P36349	NS1_I02A0	★	Non-structural protein 1	NS	Influenza A virus (strain A/Chicken/Brescia/1902 H7N7)	230
☐	P08272	NS1_I56A2	★	Non-structural protein 1	NS	Influenza A virus (strain A/Duck/England/1/1956 H11N6)	230
☐	P08276	NS1_I71A2	★	Non-structural protein 1	NS	Influenza A virus (strain A/Turkey/Oregon/1971 H7N3)	230
☐	P26148	NS1_I82A2	★	Non-structural protein 1	NS	Influenza A virus (strain A/Camel/Mongolia/1982 H1N1)	90
☐	P69278	NS1_I000W	★	Non-structural protein 1	NS	Influenza A virus (strain A/Wa-182)	237
☐	P08274	NS1_I24A0	★	Non-structural protein 1	NS	Influenza A virus (strain A/Chicken/Japan/1924 H7N7)	227
☐	P30909	NS1_I49A0	★	Non-structural protein 1	NS	Influenza A virus (strain A/Chicken/Germany/n/1949 H10N7)	230
☐	Q84056	NS1_I57A4	★	Non-structural protein 1	NS	Influenza A virus (strain A/RI/5-/1957 H2N2)	89
☐	P21431	NS1_I60A0	★	Non-structural protein 1	NS	Influenza A virus (strain A/Ann Arbor/6/1960 H2N2)	217
☐	P08278	NS1_I61A0	★	Non-structural protein 1	NS	Influenza A virus (strain A/Tern/South Africa/1961 H5N3)	227
☐	P30911	NS1_I63A1	★	Non-structural protein 1	NS	Influenza A virus (strain A/Turkey/Canada/1963 H6N8)	230
☐	P08270	NS1_I63A3	★	Non-structural protein 1	NS	Influenza A virus (strain A/Duck/Ukraine/1/1963 H3N8)	227
☐	P69277	NS1_I68A0	★	Non-structural protein 1	NS	Influenza A virus (strain A/Aichi/2/1968 H3N2)	237
☐	P30912	NS1_I72A6	★	Non-structural protein 1	NS	Influenza A virus (strain A/Tern/Turkmenia/18/1972 H3N3)	230
☐	P69252	NS1_I76A0	★	Non-structural protein 1	NS	Influenza A virus (strain A/Anas acuta/Primorje/695/1976 H2N3)	230
☐	P13137	NS1_I76A5	★	Non-structural protein 1	NS	Influenza A virus (strain A/Mallard/Alberta/88/1976 H3N8)	230

检索词为：(NS1 AND taxonomy:“Influenza A virus [11320]”)
AND reviewed:yes仍有250条序列

所选取NS1在Swiss-prot的登录号为：
P03496

Names and origin

Protein names	*Recommended name:* **Non-structural protein 1** Short name=NS1 *Alternative name(s):* NS1A
Gene names	Name:**NS**
Organism	**Influenza A virus (strain A/Puerto Rico/8/1934 H1N1)**
Taxonomic identifier	211044 [NCBI]
Taxonomic lineage	Viruses › ssRNA negative-strand viruses › Orthomyxoviridae › Influenzavirus A
Virus host	Aves [TaxID: 8782] Homo sapiens (Human) [TaxID: 9606] Sus scrofa (Pig) [TaxID: 9823]

Protein attributes

Sequence length	230 AA.
Sequence status	Complete.
Protein existence	Evidence at protein level

Secondary structure

PDB登录号：3o9s

Journal of General Virology (2008), **89**, 2359–2376 DOI 10.1099/vir.0.2008/004606-0

Review

The multifunctional NS1 protein of influenza A viruses

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[1]Centre for Biomolecular Sciences, University of St Andrews, St Andrews, Fife KY16 9ST, UK

[2]Centro Nacional de Biotecnología (CSIC), Campus de Cantoblanco, 28049 Madrid, Spain

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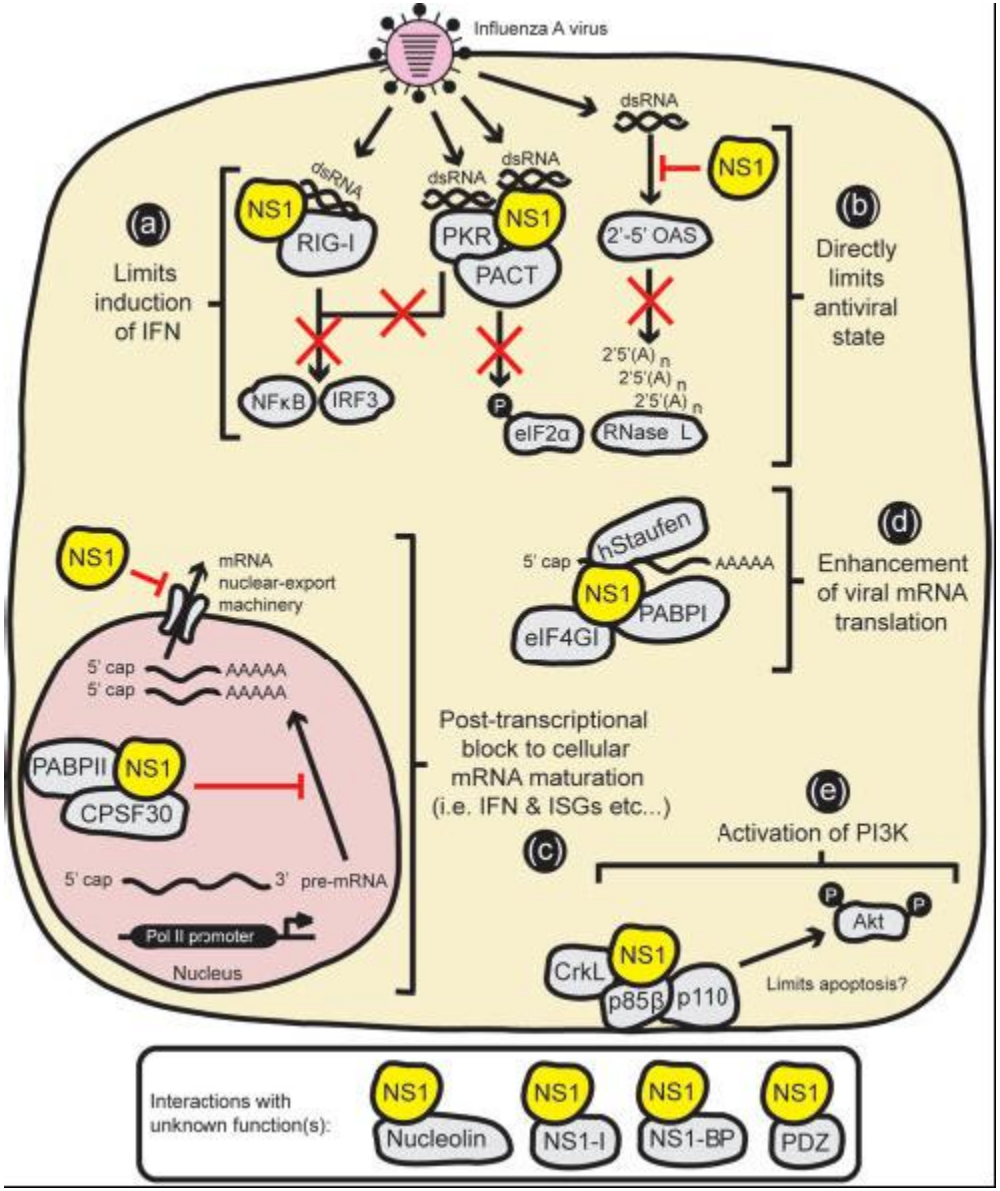
The non-structural (NS1) protein of influenza A viruses is a non-essential virulence factor that has multiple accessory functions during viral infection. In recent years, the major role ascribed to NS1 has been its inhibition of host immune responses, especially the limitation of both interferon (IFN) production and the antiviral effects of IFN-induced proteins, such as dsRNA-dependent protein kinase R (PKR) and 2'5'-oligoadenylate synthetase (OAS)/RNase L. However, it is clear that NS1 also acts directly to modulate other important aspects of the virus replication cycle, including viral RNA replication, viral protein synthesis, and general host-cell physiology. Here, we


Influenza A virus
dsRNA
dsRNA
dsRNA
dsRNA
NS1
RIG-I
PKR
PACT
2'-5' OAS
(a)
Limits induction of IFN
(b)
Directly limits antiviral state
NFκB
IRF3
P
eIF2α
2'5'(A) n
2'5'(A) n
2'5'(A) n
RNase L
NS1
mRNA nuclear-export machinery
5' cap
AAAAA
5' cap
AAAAA
PABPII
NS1
CPSF30
5' cap
3'
pre-mRNA
Pol II promoter
Nucleus
Post-transcriptional block to cellular mRNA maturation (i.e. IFN & ISGs etc...)
(c)
5' cap
hStaufen
AAAAA
NS1
eIF4GI
PABPI
(d)
Enhancement of viral mRNA translation
(e)
Activation of PI3K
P
P
Akt
CrkL
NS1
p85β
p110
Limits apoptosis?
Interactions with unknown function(s):
NS1
Nucleolin
NS1
NS1-I
NS1
NS1-BP
NS1
PDZ

ISG15 conjugation system targets the viral NS1 protein in influenza A virus–infected cells

Chen Zhao, Tien-Ying Hsiang, Rei-Lin Kuo, and Robert M. Krug[1]

Institute for Cellular and Molecular Biology, Section of Molecular Genetics and Microbiology, University of Texas at Austin, TX 78712

Edited by Alexander Varshavsky, California Institute of Technology, Pasadena, CA, and approved December 21, 2009 (received for review August 11, 2009)

ISG15 is an IFN-α/β–induced, ubiquitin-like protein that is conjugated to a wide array of cellular proteins through the sequential action of three conjugation enzymes that are also induced by IFN-α/β. Recent studies showed that ISG15 and/or its conjugates play an important role in protecting cells from infection by several viruses, including influenza A virus. However, the mechanism by which ISG15 modification exerts antiviral activity has not been established. Here we extend the repertoire of ISG15 targets to a viral protein by demonstrating that the NS1 protein of influenza A virus (NS1A protein), an essential, multifunctional protein, is ISG15 modified in virus-infected cells. We demonstrate that the major ISG15 acceptor site in the NS1A protein in infected cells is a critical lysine residue (K41) in the N-terminal RNA-binding domain (RBD). ISG15 modification of K41 disrupts the association of the NS1A RBD domain with importin-α, the protein that mediates nuclear import of the NS1A protein, whereas the RBD

example, antivirus activity has not been detected against vesicular stomatitis virus and lymphocytic choriomeningitis virus (8).

The mechanism by which ISG15 conjugation inhibits the replication of influenza virus or any other virus has not been established. Here we extend the repertoire of ISG15 targets to a viral protein by demonstrating that the NS1 protein of influenza A virus (NS1A protein) is targeted by IFN-induced ISG15 conjugation in virus-infected cells. The NS1A protein is an essential viral protein consisting of two functional domains: the N-terminal RNA-binding domain (RBD, residues 1–73) and the effector domain (residues 74–end) (16). The RBD domain of NS1A protein binds double-stranded RNA (dsRNA) (17–19) and also contains a nuclear localization signal (NLS) that binds importin-α (20). We show that the major ISG15 attachment site is a critical lysine residue (K41) in the RBD and that this ISG15 modification disrupts the association

ISG15 Modification of K41 of the NS1A Protein Inhibits Influenza A Virus Replication. To determine whether ISG15 modification of K41 of the NS1A protein inhibits influenza A virus replication, it was essential to use a virus that encodes an NS1A protein with only one NLS, the one containing K41. The NS1A protein encoded by the H1N1 influenza A/WSN/33 virus (WSN) is such an NS1A protein. In cells pretreated with IFN-β (+IFN), the WSN NS1A protein was ISG15 modified to a similar extent in cells infected with the WSN virus or with a Ud recombinant virus in which the Ud NS gene was replaced by the WSN NS gene (Ud/NS-WSNWT) (Fig. 4*A*, lanes 2 and 3). A K41R substitution in the WSN NS1A protein in the Ud recombinant virus (Ud/NS-WSNK41R) led to an 80–90% decrease in ISG15 conjugation of the NS1A protein (Fig. 4*A*, lane 4), demonstrating that K41 is the major ISG15 modification site of the WSN NS1A protein in infected cells.

Idea

小组的思路：

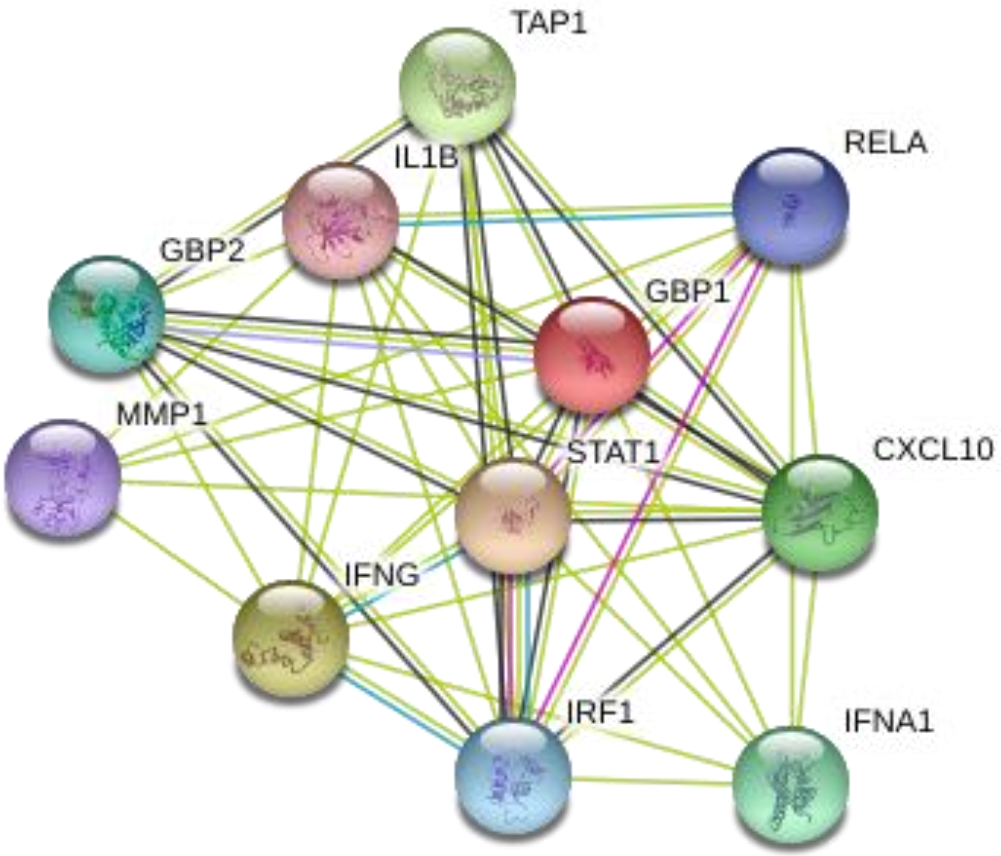
1.分别寻找与hGBP1和NS1互作的蛋白质；

2.比对分析NS1与hGBP1互作蛋白质之间的氨基酸序列及空间结构

比对分析hGBP1与NS1互作蛋白质之间的氨基酸序列及空间结构

3.通过基序分析程序寻找hGBP1可能存在的与NS1互相作用的关键位点

与hGBP1互作的蛋白质



引自http://string-db.org/newstring_cgi/show_network_section.pl

consultation

Sequence	Alignment
	- - - - - - - - - - - - - - - - - M D P N T V S S F Q V D C F L W H V R K R - V A D Q E L G D A P F L
1. NS1 I34A1	- - - - - - - - - - - - - - - - - . . . . - . . . .
2. IL1B HUMAN	- - - - - - - - - - - - - - - - - - - M A E . P E L A S E M M A Y Y S G N - E . D L F F E . D G P
3. RELA HUMAN	- - - - - - - M D E L F P L I F P A E . A Q A . G P Y . E I I E Q P K Q R - - - - - - - - - - - - - - - - - G M R F R Y K C . G R S . G S I
4. CXCL10 HUMAN	- M N Q T A I L I C . L I F L T L S - G I
5. GBP2 HUMAN	I D N T K G Q L V V N P E A L K I L S A I . Q P V V V . A I V G L Y R T G - - - - - - - - - - - - - - - - - - K S Y L M N K L A . K K N G F
6. IFNG HUMAN	- - - - - - - - - - - - - - - - - . K Y T S Y I L A F Q L . I V L G S L G - - - - - - - - - - - - - - - - - - - C Y C Q . P Y V K E . E N .
7. IRF1 HUMAN	- - - - - - - M P I T R M R M R P W L E M Q I N . N . I P G L I . I N K E - E M I F Q I P W K H A A
8. TAP1 HUMAN	L A D W V L L R T A L P R I F S L L V . T A L P L L R . W A V G L S R W A V L W L G A C G V L R A T V G S K S E N A G . Q G W . A A L K P .
9. IFNA1 HUMAN	- - - - - - - - - - - - - - - - M A S . F A - - - L L M V L V V L S C K S - - - - - - - - - - - - - - - - - - - S C S L G C D . P E T H S .
10. MMP1 HUMAN	- - - - - - - M H S F P P L L L L L F W G V . . H S F P A T L E T Q E Q D - - - - - - - - - - - - - - - - - - - V D L V Q K Y . E K Y Y N .
11. STAT1 HUMAN	E N N F L L Q H N I R K S K R N L Q . N F Q E D P I . M S M I I Y S C L . E E R K - - - - - - - I L E N A Q R F N Q A Q S G N I Q S T V M .

Sequence	Alignment
	- - - - R Y L T D M T L E E M S R D W S M L I P K Q K V A G P L C I R M D Q A I M D K N I I L K A N F S V I F D R L E T - - - - - - - - - -
1. NS1 I34A1	- - - - . . . . - - - - - - - - - -
2. IL1B HUMAN	I F E E E P I F F D . W D N - - - - - E A Y V H D A P . R S L N . T L R . S Q Q K S L V M S G P Y E L K A L H L Q G Q D - - - - - - - - - -
3. RELA HUMAN	N A V R L C F Q V T V R D P S G . P L R L P P V L S H P I F D N R A P N T A E L K I C R V N R N S G S C L G G . E I F L L C D - - - - - - -
4. CXCL10 HUMAN	- - - - - - - - V E I I A T . K K K G E K R C L N - - - - - - - - - P E S K . . K N L L K A V S K E R . K R S P - - - - - - - - - - - - - -
5. GBP2 HUMAN	D D S A D - - F V S F F P A F V W T L R D F T L E L E . D . E P - - I T A D D Y L E L S L K . R K G T D K K S K S F N D - - - - - - - - - -
6. IFNG HUMAN	D M N V K - - F F N S N K K K R D . F E K . T N Y S V T D L N V Q R K A I H E L I Q V M A E . S P A A K T G K R K R S Q - - - - - - - - - -
7. IRF1 HUMAN	P P L T K N Q R K E R K S K S . . . A K S K A K R K S C G D S S P D T F S D G L S S S T L P D D H S S Y T V P G Y M Q D - - - - - - - - - -
8. TAP1 HUMAN	E F V G D G I Y N N . M G H V H S H L Q G E V F G A V L R Q E T E F F Q Q N Q T G N I M S R V T E D T . T L S . S . S E N L S L F L W Y L V
9. IFNA1 HUMAN	D L L D K - - F C T E . Y Q Q L N . L E A C V M Q E E R V . E T P L M N A D S . L A V K K Y F R R I T L Y L T E K K Y S - - - - - - - - - -
10. MMP1 HUMAN	N Y T P D L P R A D V D H A I E K A F Q L W S N V T P L T F T K V S E G Q A D . . I S F V R G D H R D N S P . . G P G G - - - - - - - - - -
11. STAT1 HUMAN	D Q L Q N - - W F T I V A . S L Q Q V R Q Q L K . L E E L E Q K Y T Y E H D P . T K N K Q V . W D R T F S L . Q Q . I Q S S - - - - - - - F

Sequence	Alignment
	- - - - - H T A E D V K N A V G V L I G G L E W N D N T V R V S E T L Q R F A W R S S N E N G -
1. NS1 I34A1	- - - - - . . . . -
2. IL1B HUMAN	- - - - - - P T L Q L E S V D P K N Y P K K K M E K R F . F N K I E I N - N K L
3. RELA HUMAN	V S M Q L R R P S . R E L S E P M E F Q Y . P D T . D R H . I E . K R K . T Y E T F K S I M K - K S
4. CXCL10 HUMAN	- -
5. GBP2 HUMAN	V N G P R L E S L V L T Y V N A I S S . D . P C M E . A . L A L A Q I E N S . A V E K A I A H - - - - - - - - - - - - - Y E Q Q M G Q K V
6. IFNG HUMAN	- -
7. IRF1 HUMAN	- - - - P M P S T S E A T T D E D E E . K . P E D I M K L L E Q S E W . P T N V D G K G Y - L L
8. TAP1 HUMAN	F R E K L Q E I K T L N Q K E A . A Y A V N S . T T S I S G M L L K V G I L Y I G G Q L V T S G A V S S G N L V T F V L Y Q M Q F T Q A V
9. IFNA1 HUMAN	- -
10. MMP1 HUMAN	- - - - - L G L S H S T D I G A L M Y P S Y T F S G D V Q L A Q D D I D G I Q A I Y G R S Q N - P V
11. STAT1 HUMAN	T N G S L A A E F R H L Q L K E Q K N A . T R T . E G P L I . T . E . H S L S F E T Q L C Q P - - - - - - - - - - - - - G L V I D L E T T

与NS1互作的蛋白质

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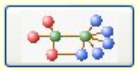
Phosphatidylinositol 3-kinase regulatory subunit beta

Binary Interactions
MINT viewer



UniProtKB AC	O00459, Q5EAT5, Q9UPH9,
Organism	Homo sapiens (9606)
genenames and synonyms	PIK3R2, Phosphatidylinositol 3-kinase , Phosphatidylinositol 3-kinase ,
Domains	PI3kinase_P85 (IPR001720), RhoGAP (IPR000198), SH2 (IPR000980), SH3 (IPR001452), (IPR008936),
diseases	OMIM: (603157),
Gene Ontology	F:protein binding GO:0005515 negative regulation of anti-a GO:0019987 GO:0005942 GO:0035014 GO:0007165
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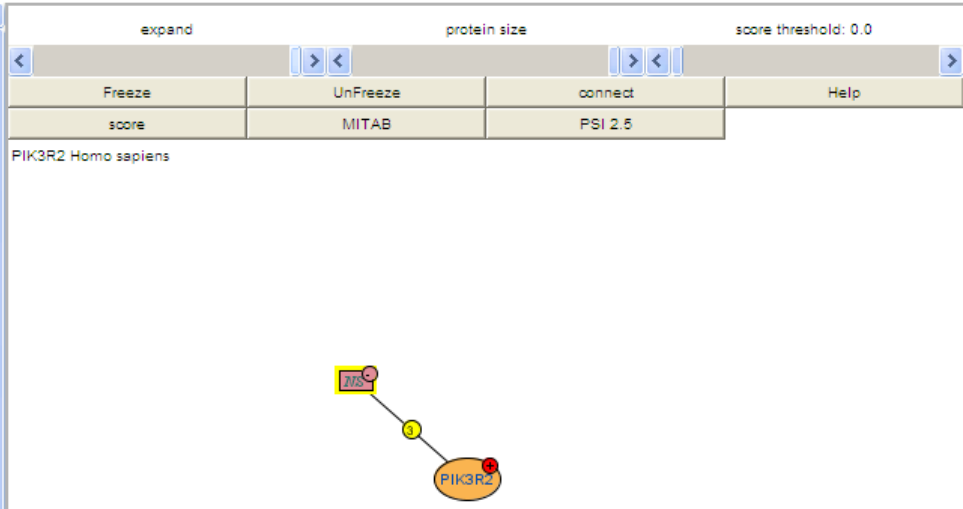

Database of Interacting Proteins

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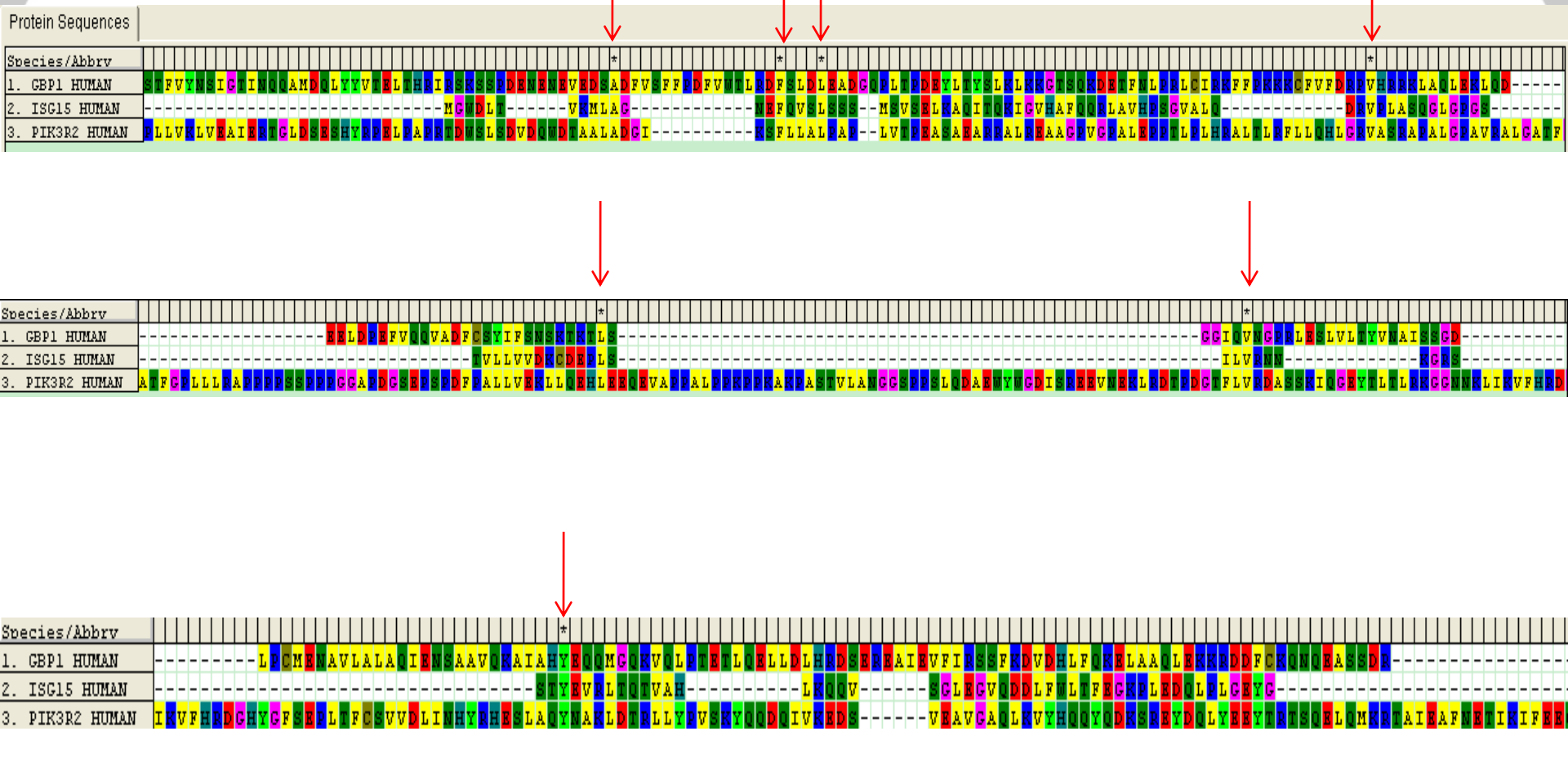
DIP 29081N

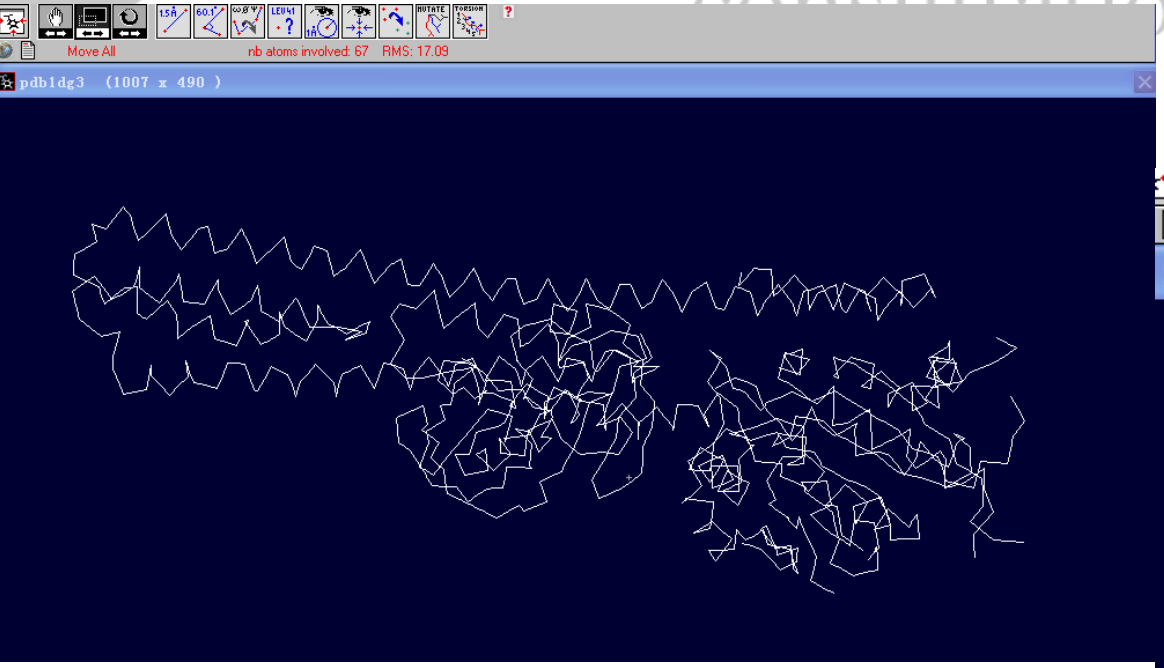
BROWSE LINKS

Protein: Non-structural protein 1

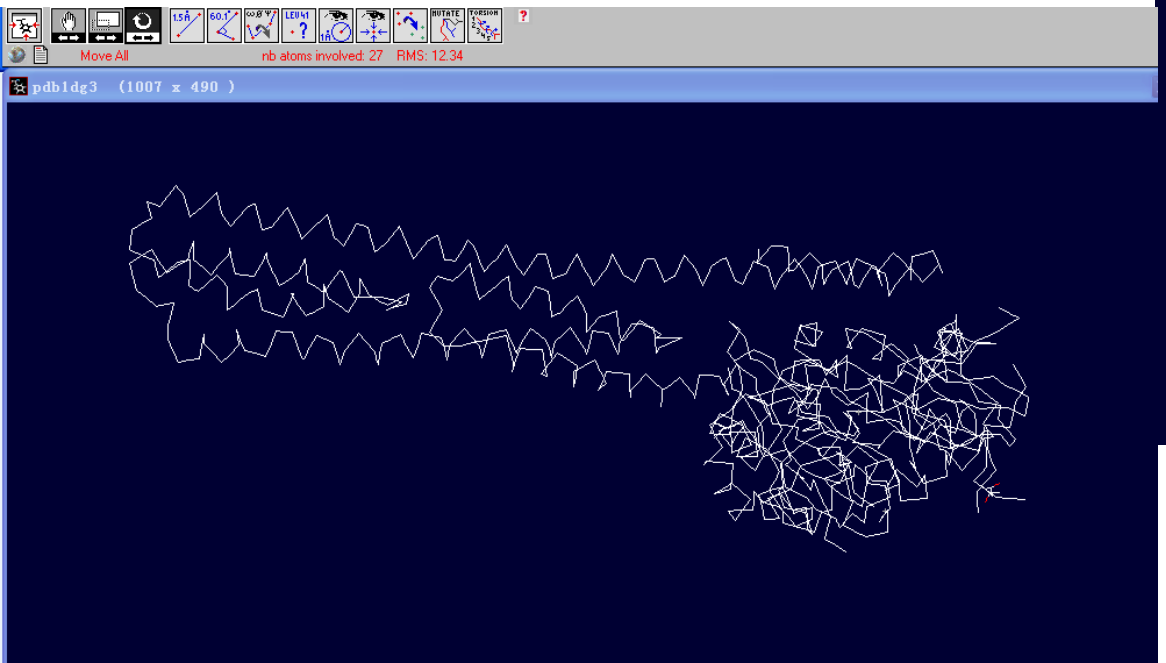
Binary | Complex | Functional

DIP			Cross Reference			Protein Name/Description
Interaction	Interactor(s)	Links	PIR	SWISSPROT	GENBANK	
DIP:57082E	DIP:29081N		---	P03496	---	Non-structural protein 1
DIP:185521E	DIP:39878N		---	P23726	---	Phosphatidylinositol 3-kinase regulatory subunit beta


Protein Sequences
Species/Abbrv
1. GBP1 HUMAN
2. ISG15 HUMAN
3. PIK3R2 HUMAN

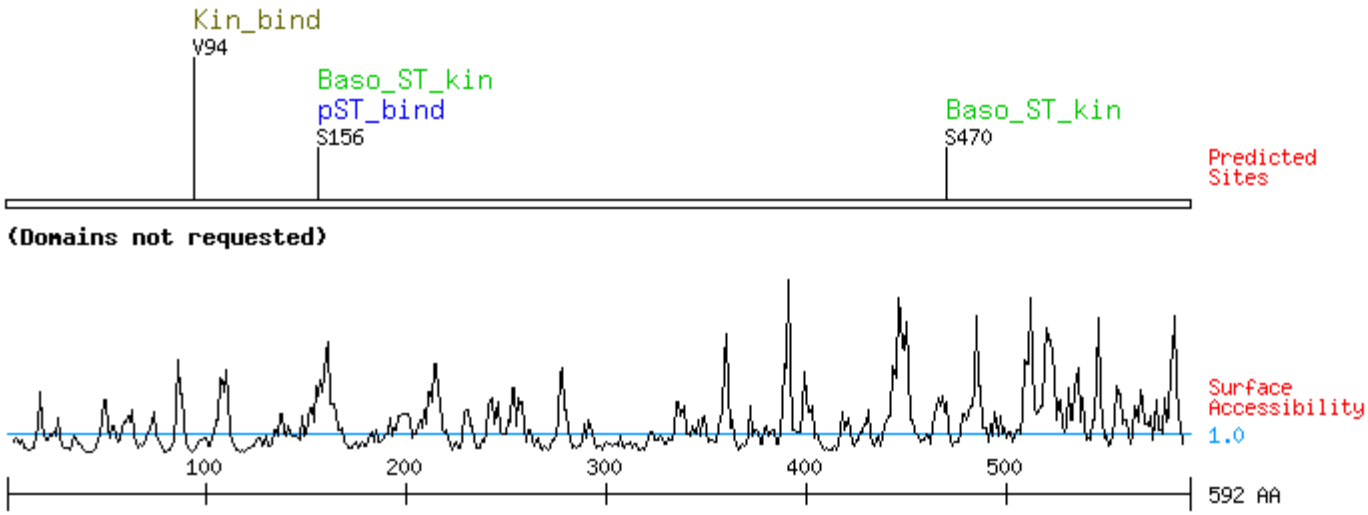

Move All
nb atoms involved: 67
RMS: 17.09
pdb1dg3 (1007 x 490)


Move All
nb atoms involved: 27
RMS: 8.56
1Z2 (1007 x 490)


Move All
nb atoms involved: 27
RMS: 12.34
pdb1dg3 (1007 x 490)

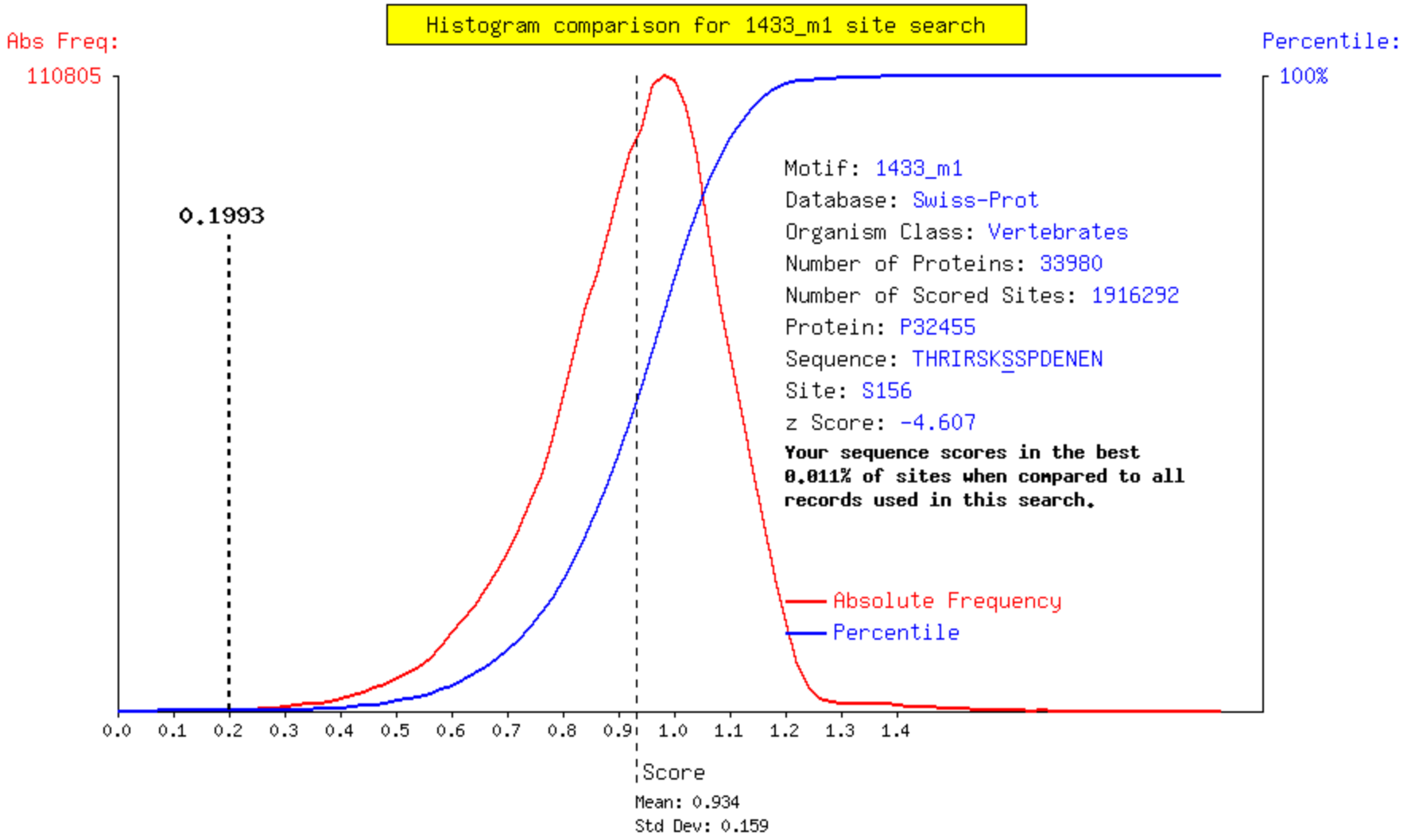
	RMSD	匹配位点数		
3O5Z-1Z2M	8.56	27位	3O5Z B链21-47	1Z2M A链43-69
3O5Z-1DG3	12.34	27位	3O5Z A链77-B链23	1DG3 A链116-142
1Z2M-1DG3	17.09	67位	1Z2M A链7-73	1DG3 A链301-340、343-369

注： 3O5Z代表pIK3R2, 1Z2M代表ISG15, 1DG3代表hGBP1



使用Scansite对hGBP1(1DG3)进行基序预测

Phosphoserine/threonine binding group (pST_bind)				
14-3-3 Mode 1			Gene Card YWHAZ	
Site	Score	Percentile	Sequence	SA
S156	0.1993	0.011 %	THRIRSKSSPDENEN	2.848
Basophilic serine/threonine kinase group (Baso_ST_kin)				
PKC epsilon			Gene Card PRKCE	
Site	Score	Percentile	Sequence	SA
S470	0.3526	0.054 %	TYLKSKESMTDAILQ	2.537
Akt Kinase			Gene Card AKT1	
Site	Score	Percentile	Sequence	SA
S156	0.4630	0.132 %	THRIRSKSSPDENEN	2.848
Kinase binding site group (Kin_bind)				
Erk D-domain			Gene Card MAPK1	
Site	Score	Percentile	Sequence	SA
V94	0.4720	0.024 %	KKPGHILVLLDTEGL	0.112



Note: Although the distribution is similar to a normal for searches with many sites, the percentile reported here is computed directly from the histogram, and not from a z table.

引自http://scansite.mit.edu程序分析

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PLoS one

Human Guanylate Binding Proteins Potentiate the Anti-Chlamydia Effects of Interferon-γ

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University of Louisville M
Biology, Imperial Colleg

and Immunology,
Cell and Molecular

Abstract

Chlamydiae ar
murine p47 GT
the human ge
findings to ch
guanylate binc
the inclusion m
statistically sig
chlamydial act
potentiate the
increase in inc
version of the

-inducible
o. Because
47 GTPase
he human
localize to
e mild, but
otent anti-
appear to
led to an
full-length
d by hGBP

membrane [30,31]. In the same report, the murine homologue (Irga6) of Iigp1 was found to be dispensable in the resistance to chlamydia infection [28], a finding that is in conflict with that reported by Al-Zeer *et al* [32]. It is possible that a functional redundancy among these p47 GTPases exists and that the role of Iigp1 is masked *in vivo*. The p47 GTPase orthologues present in the human genome, IRGC and IRGM, are not inducible by IFN-γ [33,34]. IRGC is also presumed to be a pseudogene. Interestingly, humans do not possess a p47 GTPase-based resistance. Thus, the importance of the findings in murine models of infection is unclear. The presence of hGBPs in the human genome, in conjunction with its lack of genes encoding p47 GTPases suggests that some function of the p47 GTPases in mice may be mediated by hGBPs in humans. To address this hypothesis, the relationship between hGBPs and chlamydial growth in cultured cells was characterized. We report that hGBPs link IFN-γ with its inhibition of chlamydial growth by acting as a potentiator, rather than an effector of the anti-chlamydial function of this cytokine.

reference

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THANK YOU FOR YOUR ATTENTION!