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Modeling of apoptin protein

Manjusha Tyagi

Department of Microbiology, SGRR University, Dehradun

Email: manjushatyagi20008@gmail.com

Abstract

Modeling of apoptin protein of chicken anemia virus was done and valuable structural details could be revealed.

Key words: Apoptin, chicken anemia virus VP3, protein modeling

Introduction

VP3 of chicken anemia virus, also called as apoptin, is a 13 kDa protein that shows apoptic activity and is able to induced apoptosis within infected chicken cells and human tumor cell lines (Noteborn *et al.,* 2004). VP3 also named apoptin, a nonstructural protein encoded by the VP3 gene of chicken anemia virus (CAV), has been shown to not only induce apoptosis when introduced into the precursors of chicken thymocytes, but has been found to specifically kill human cancer cells tumor cells, and transformed cells without affecting the proliferation of normal cells (Lee *et al.,* 2012). Modeling of this protein could reveal valuable useful information.

Materials and Methods

Protein sequence

Chicken anemia virus apoptin (vp3) gene, complete cds GenBank: AY171617.1 linear 366 bp DNA was downloaded and used the amino acid sequence for modeling. The submitted primary amino acid sequence is given in Table 1.

Table 1.

Primary amino acid sequence for which templates were searched and models were built.

MNALQEDTPPGPSTVFRPPTSSRPLETPHCREIRIGIAGITITLSLCGCANARAPTLRSATADNS
ESTGFKNVPDLRTDQPKPPSKKRSCDPSEYRVSEL
KESLITTTPSRPRTARRRIRL

Model Building

Models are built based on the target-template alignment using ProMod3 (Studer et al.,2020.). Coordinates which are conserved between the target and the template are copied from the template to

the model. Insertions and deletions are remodelled using a fragment library. Side chains are then rebuilt. Finally, the geometry of the resulting model is regularized by using a force field.

Model Quality Estimation

The global and per-residue model quality has been assessed using the QMEAN scoring function (Studer et al.. 2020.).

Ligand Modelling

Ligands present in the template structure are transferred by homology to the model when the following criteria are met: (a) The ligands are annotated as biologically relevant in the template library, (b) the ligand is in contact with the model, (c) the ligand is not clashing with the protein, (d) the residues in contact with the ligand are conserved between the target and the template. If any of these four criteria is not satisfied, a certain ligand will not be included in the model. The model summary includes information on why and which ligand has not been included.

Oligomeric State Conservation

The quaternary structure annotation of the template is used to model the target sequence in its oligomeric form. The method (Bertoni et al., 2017.) is based on a supervised machine learning algorithm, Support Vector Machines (SVM), which combines interface conservation, structural clustering, and other template features to provide a quaternary structure quality estimate (QSQE). The QSQE score is a number between 0 and 1, reflecting the expected accuracy of the interchain contacts for a model built based a given alignment and template. Higher numbers indicate higher reliability. This complements the GMQE score which estimates the accuracy of the tertiary structure of the resulting model.

Results and Discussion

Template Results

A total of 19 templates were found to match the target sequence. This list was filtered by a heuristic down to 8 (table 2).

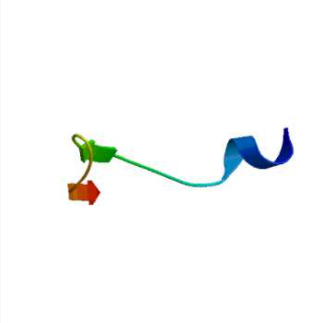
Table 2.

Template	Seq Identity	Oligo-state	QSQE	Found by	Method	Resolution	Seq Similarity	Coverage	Description
4rrp.2.C	16.67	monomer	-	HHblits	X-ray	2.79Å	0.28	0.20	Antigen Asf1p
2ygv.1.A	16.00	monomer	-	HHblits	X-ray	2.94Å	0.27	0.21	Histone chaperone ASF1
2ygv.3.A	16.00	monomer	-	HHblits	X-ray	2.94Å	0.27	0.21	Histone chaperone ASF1
5ucb.1.C	16.00	monomer	-	HHblits	X-ray	1.52Å	0.27	0.21	Histone chaperone ASF1
4eo5.1.A	16.00	monomer	-	HHblits	X-ray	2.35Å	0.27	0.21	Histone chaperone ASF1
4rrp.1.C	16.67	monomer	-	HHblits	X-ray	2.79Å	0.28	0.20	Antigen Asf1p
1roc.1.A	16.00	monomer	-	HHblits	X-ray	1.50Å	0.27	0.21	Anti-silencing protein 1
1wg3.1.A	15.38	monomer	-	HHblits	X-ray	3.00Å	0.27	0.21	Anti-silencing protein 1

The top templates are:

Template	Sequence Identity	Biounit Oligo State	Description
4rrp.2	16.67	hetero-trimer	Antigen Asf1p Crystal Structure of the Fab complexed with antigen Asf1p, Northeast Structural Genomics Consortium (NESG) Target PdR16
2ygv.1	16.00	hetero-dimer	HISTONE CHAPERONE ASF1 Conserved N-terminal domain of the yeast Histone

Template	Sequence Identity	Biounit Oligo State	Description
			Chaperone Asf1 in complex with the C-terminal fragment of Rad53
2ygv.3	16.00	hetero-dimer	HISTONE CHAPERONE ASF1 Conserved N-terminal domain of the yeast Histone Chaperone Asf1 in complex with the C-terminal fragment of Rad53
5ucb.1	16.00	hetero-trimer	Histone chaperone ASF1 Structure of antigen-Fab complex with engineered switch residue region.
4eo5.1	16.00	hetero-trimer	Histone chaperone ASF1 Yeast Asf1 bound to H3/H4G94P mutant

	Id	Template	GMQE	QMEANDisCo Global	Oligo State	Ligands
	01	4rrp.2.C	0.00	0.09 ± 0.12	monomer	-

Models

The following model was built.

Model #01	File	Built with	Oligo-State	Ligands	GMQE	QMEANDisCo Global
	PDB	ProMod3 3.2.1	monomer	None	0.00	± 0.12

Template	Seq Identity	Oligo-state	QSQE	Found by	Method	Resolution	Seq Similarity	Range	Coverage	Description
4rrp.2.C	16.67	Monomer	0.00	HHblits	X-ray	2.79Å	0.28	31 - 54	0.20	Antigen Asf1p

The template contained no ligands.

Target
MNALQEDTPPGPSTVFRPPTSSRPLETPHCREIRIGIAGITITLSLCGCANARAPTLRSATADNS
ESTGFKNVPDLRTDQ
4rrp.2.C ----------ASELVSVTVILLSCSYDGREFVRV----------

Target PKPPSKKRSCDPSEYRVSELKESLITTTPSRPRTARRRIRL
4rrp.2.C ----------

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