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GENOMICS, PROTEOMICS AND DRUG DESIGNING APPROACHES ON AVIAN LEUKEMIA VIRUS

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ABSTRACT:

Avian Leukemia Virus (A LV) belongs to Retroviridae family. The complete genome of ALV contains 7489 bp of length with Accession number HQ425636 of NCBI. Five genes are predicted by Viral prediction server, FGENESV0. Gag, pol and env are the proteins predicted based on sequence alignment. Granulocyte macrophage colony stimulating factor has shown good activity on Gag polyprotein (R.value 20.8). IGG2A intact antibody has shown good activity against pol polyprotein. Interferon alfa2B has shown better activity, forming complex with pol polyprotein (R Value 5.6, E,Total -573.81). IGG2A antibody has also shown better activity in deactivating envelop protein of ALV (R=8.8, E.Total = -496.11). Vindesine, altretinoin, Imatanib, Etoposide, Docetaxel, Flavopiridol has shown good activity against Gag, Poly, Env proteins of ALV.

Keywords: Avian Leukemia Virus, Gene prediction, Docking

[I] INTRODUCTION

Avian leukemia Virus (ALV) functions as a potent RNA export signal are replication-defective avian retroviruses that contain the *myb* oncogene and cause leukemia in chickens [1]. Leukemia is a progressive and malignant disease of the vertebrate organs, marked by distorted proliferation and development of leukocytes and their precursors in the blood, bone marrow and thymus [2]. Avian leukemia virus E26 causes both erythroid and myeloid tumors in chickens, due to the presence of a tripartite gene encoding a 135-kDa protein containing gag, v-myb, and v-ets sequences [3].

The genome of avian leukemia virus E26 shares homology with v-myb, the oncogene of avian myeloblastosis virus, and encodes a protein with an Mr of 135,000[4]. Isolation and characterization of four E26 temperature-sensitive (*ts*) mutants for myeloblast transformation associate with level of expression of the provirus [5.6]. E26-transformed myeloid cells bear a resemblance to macrophage precursors and proliferate rapidly, provided the favourable growth medium contains chicken myelomonocytic growth factor (cMGF).

The Avian leukemia-inducing oncogenes,are mutated forms of cellular proteins. leukemia viruses are relatively common in chickens and may have susceptibility to the transforming effects of a variety of oncoproteins [7]. Replication-defective avian leukemia viruses (DLVs) are a group of oncoviruses isolated from the domestic chicken that are capable of causing acute leukemias. The unique property of these viruses is their specificity of transformation in the hematopoietic system *in vivo* and *in vitro*[8].

Retroviral replication requires the host cell to generate spliced [9, 10]. unspliced, and, in some cases, partially spliced viral mRNAs. Hence retroviruses rely on RNA must therefore contain recognizable splicesites [11,12,13].

Genomics, Proteomic, Molecular modeling and Drug designing are new emergent areas of science that uses computational approaches to answer biological problems. In the twentieth first century, a major research goal is to find the functions of genes obtained from genomes and to

define their interactions in a particular organism obtained by experiment at faster rate. The scientific investigations take advantage of large, complex data sets in a vigorous fashion to achieve valid, biological conclusions [14,15].

[II] MATERIALS AND METHODS

2.1. System requirements

In this work, we attempted to carry out the Analysis of protein and drug designing with the following infrastructure.

1. **SYSTEM USED** –Intel Pentium 4 GHz, 2GB RAM
2. **OPERATING PLATFORM**- Microsoft Windows XP pro 2002 service pack
3. **SOFTWARE PACKAGES** – HEX 5.1,

2.2. Viral gene identification

Genome sequence for ALV has been submitted to FGENEV0 for identification of number of genes present in the genome. The sequences are identified based on alignment of the proteins using BLASTP.

2.3. Protein Characterization

The molecular weights and pI of the predicted proteins are characterized using ExPASy tools. (http://expasy.org/tools/pi_tool.html)

2.4. Docking studies

Various ligands are selected from DrugBank. Antibodies against ALV are selected from PDB. Predicted protein sequences of ALV is modeled using SWISSMODEL.

Hex is an interactive molecular graphics program used for calculating and displaying feasible docking modes of pairs of protein. Hex can also calculate protein-ligand docking, assuming the ligand is rigid, and it can superpose pairs of molecules using only knowledge of their 3D shapes.

[III] RESULTS

3.1. Gene identification

The genome of ALV has been retrived from GenBank database of NCBI with Accession number HQ425636 contains 7489 bp of length. Gene prediction from the genome of ALV provides information of proteins, which can be translated. FGENESV0 prediction server (Figure 1) has shown 5 genes to ALV genome.

3.2. Gene characterization:

Table 1 has shown characterization of the genes predicted in FGENESV0. The five predicted proteins are gag, pol, env, hypothetical and unidentified protein.

FGENESV0: Prediction of potential genes in viral genomes
Seq name: ALV
Length of sequence - 7489 bp
Number of predicted genes - 5

N	S		Start		End	Score
1	+	CDS	593	-	2698	2106
2	-	CDS	2634	-	2855	222
3	+	CDS	3025	-	5337	2313
4	-	CDS	3543	-	4334	792
5	+	CDS	5267	-	6988	1722

Figure: 1. Gene identification of ALV

3.3. Docking

(Table 2) Granulocyte macrophage colony stimulating factor has shown good activity on Gag polyprotein (R.value 20.8). IGG2A intact antibody has shown good activity against pol polyprotein. Interferon alfa2B has shown better activity, forming complex with pol polyprotein (R Value 5.6, E,Total -573.81). IGG2A antibody has also shown better activity in deactivating envelop protein of ALV (R=8.8, E.Total= -496.11).

Vindesine, altretinoin, Imatanib, Etoposide, Docetaxel, Flavopiridol has shown good activity against Gag, Poly, Env proteins of ALV.

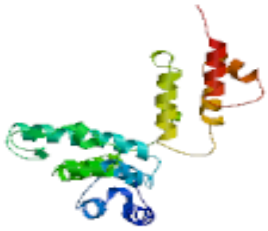
Protein No.	Characterization	3D Model of Protein (Swiss Model)	pI	MW
1	**gag polyprotein**		8.53	74414.08
2	**No significant similarity found**	No suitable templates found	8.53	7567.59
3	**pol polyprotein**		8.82	92375.43
4	**Hypothetical protein**	No suitable templates found	10.52	27603.71
5	**envelope protein**		8.42	63702.92

Table: 1. Gene identification and Charecterization of ALV

S. No	Ligands	Protein Receptors					
		gag polyprotein		pol polyprotein		envelope protein	
		R Value	E.Total	R Value	E.Total	R Value	E .Total
1	anti-CD52 (CAMPATH-1)	32.8	-736.64	23.2	-719.45	16.8	-513.13
2	IGG2A INTACT ANTIBODY	36.8	0	12.8	-689.75	8.8	-496.11
3	INTERFERON ALPHA-2A	62.3	0	-	-	-	-
4	PUTATIVE L-ASPARAGINASE	51.2	0	48.9	0	12.8	-256.52
5	Granulocyte-Macrophage Colony-Stimulating Factor	20.8	-1	31.9	0	33.5	-1
6	L-asparaginase II	30.4	-608.71	52.0	0	34.0	0
7	INTERFERON-ALPHA 2B	32.0	0	5.6	-573.81	12.8	-368.15
8	Cladribine	22.4	-172.54	14.4	-153.14	18.6	-145.21
9	Anagrelide	21.6	0	24.5	-186.56	30.0	-1
10	Chlorambucil	16.8	-197.93	32.0	0	4.8	0
11	Vindesine	6.4	-255.51	12.5	-156.52	18.0	0
12	Thioguanine	19.2	0	25.5	0	32.2	0
13	Epirubicin	17.6	-226.90	-	-	7.2	0
14	Rimantadine	16.0	-136.20	32.0	0	4.8	0
15	Alitretinoin	4.0	-182.71	8.6	-289.5	5.6	0
16	Cyclophosphamide	16.8	-149.78	32.0	0	13.2	-169.52
17	Pentostatin	29.6	0	32.0	0	30.2	-1
18	Imatinib	4.0	-228.42	15.2	-228.58	8.0	-228.82
19	Clofarabine	16.8	-174.32			6.2	0
20	Prednisone	22.4	-192.46	32.0	0	34.0	0
21	Daunorubicin	18.4	-220.23	18.6	0	32.0	-1
22	Tretinoin	28.6	0	32.1	0	26.5	0
23	Etoposide	4.0	-234.68	15.2	-227.74	18.5	-256.52
24	Mechlorethamine	13.5	-118.20	-	-	16.2	-128.42
25	Azacitidine	16.0	-167.66	32.0	0	16.9	-192.23
26	Cytarabine	16.0	-160.16	23.2	0	18.2	-182.82
27	Doxorubicin	19.2	0	-	-	26.3	0
28	Hydroxyurea	19.2	-1	16.8	-90.88	5.0	0
29	Busulfan	4.2	120.40	32.0	0	8.9	-168.2
30	Mercaptopurine	19.2	0	18.6	0	17.5	0
31	Idarubicin	4.0	-208.98	-	-	12.0	-256.6
32	Paclitaxel	19.2	0	17.6	-287.40	2.4	0
33	Docetaxel	5.6	-263.15	6.8	-228.8	16.5	-248.5
34	Dasatinib	20.0	-220.42	22.0	-1	18.2	-202.8
35	Decitabine	19.2	0	5.6	0	24.6	-1
36	Nelarabine	19.2	0	20.0	0	18.6	-148.5
37	Flavopiridol	16.8	-209.57	6.1	-1	3.2	-1
38	Nilotinib	19.2	0	-	-	22.6	-206.8

Table: 2. Docking results (Protein-Protein/ Protein-Ligand)

[IV] DISCUSSION

HartmutBeug et al., 1979 was investigated on Chicken hematopoietic cells transformation *in vitro* and *in vivo* by seven strains of replication-defective avian leukemia viruses for the expression of six erythroid and five myeloid differentiation parameters, including differentiation-specific surface antigens and detected a newly developed antisera [16]

The MH2 provirus of Avian Leukemia virus measures 5.5 kb including two long terminal repeats (LTR), and contains a partial complement

of the structural gene gag, 1.5 kb in size, near the 5' terminus, and a 1.3-kb segment of the v-myc transforming gene near the 3' terminus[17]

On the basis of their oncogenic properties, avian retroviruses can be assigned to either of two major classes (nondefective avian leukemia viruses [ALVs] and defective avian leukemia viruses [DLVs])[18]. OK10 is a defective leukemia virus which shares some biological and biochemical properties of avian myelocytomatosis virus (MC29) [19].

The present study shows that the complete genome of ALV predicted five genes, where gag, pol and env play a major role as oncogens in chickens.

[V] CONCLUSION

The presence in the MH2 genome of two unrelated cell-derived sequences and their independent expression may be significant for the oncogenic specificities of avian acute leukemia virus. The genome of avian leukemia virus E26 shares homology with v-myb, the oncogene of avian myeloblastosis virus, and encodes a protein with an Mr of 135,000 [20]. In-depth research is been needed for identification and mechanism of action of ALV in chickens and their relationship with other leukemia viruses.

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REFERENCES

[1] Barbara EM, Henry RB. [1988] Transformation of avian lymphoid cells by reticuloendotheliosis virus. *Mutation Research/Reviews in Genetic Toxicology* 195(1): 79-90.

[2] Kathryn R, Hartmut, ShaulKornfeld, Thomas G. [1982] Transformation of both erythroid and myeloid cells by E26, an avian leukemia virus that contains the *myb* gene. *Cell* 31(3): 643-653.

[3] Lautenberger, and Papas T S. [1993] Inversion of a chicken ets-1 proto-oncogene segment in avian leukemia virus E26. *journal of virology* 67(1): 610-612.

[4] Ghysdael J, Gegonne A, Pognonec P, Dernis D, Leprince D, Stehelin D. [1986] Identification and preferential expression in thymic and bursal lymphocytes of a c-ets oncogene-encoded Mr 54,000 cytoplasmic protein. *PNAS* 83(6): 1714-1718.

[5] Klempnauer K H, and Bishop J M, [1984] Neoplastic transformation by E26 leukemia virus is mediated by a single protein containing domains of gag and myb genes. *Journal of virology* 50(1): 280-283.

[6] Chen JH. [1985] The proto-oncogene c-ets is preferentially expressed in lymphoid cells., *Mol Cell Biol*. 5(11): 2993-3000.

[7] Kelly M, Nagny MC, Thomas G. [2003] E26 leukemia virus converts primitive erythroid cells into cycling multilineage progenitors. *Blood* 101(3): 1103-1110.

[8] Graf T, Beug H, Hayman M J. [1980] Target cell specificity of defective avian leukemia viruses: hematopoietic target cells for a given virus type can be infected but not transformed by strains of a different type. *PNAS* 77 (1): 389-393.

[9] Stevenson M, Stanwick T L, Dempsey M P, Lamonica C A. [1990] HIV-1 replication is controlled at the level of T cell activation and proviral integration. *EMBO* 9(5): 1551–1560.

[10] Hu WS, Temin H M. [1990] Genetic consequences of packaging two RNA genomes in one retroviral particle: pseudodiploidy and high rate of genetic recombination. *PNAS* 87 (4): 1556-1560.

[11] Jin Y, Bryan RC. [1999] Structural and functional analysis of the avian leukemia virus constitutive transport element. *Cambridge Journals*. 5(12): 1645-1655.

[12] Victoria W, Pollard, Michael H M. [1998] The HIV-1 Rev Protein, *Annual reviews A Nonprofit Scintific reviews*. 52: 491-532

[13] Yang J, Cullen B R. [1999] Constitutive transport element. Structural and functional analysis of the avian leukemia virus. *RNA* 5: 1645-1655.

[14] Kaladhar DSVGK. [2011] Genomic and Proteomic studies using computational approaches in SARS genome, *IJPSRR* 7(2): 137-141.

[15] Kaladhar DSVGK, Krishna Chaitanya A. [2011] Comparative Genome Analysis using Computational Approach in HIV-1 and HIV-2. *IJCSET* 2(1): 129-132.

[16] HartmutBeug. Alexandra VK. Gabriele Döderlein, Jean-Francois C. Thomas G. [1979] Chicken hematopoietic cells transformed by seven strains of defective avian leukemia viruses display three distinct phenotypes of differentiation. *Cell* 18(2): 375-390.

[17] Jansen H W. Rückert B. Lurz R. Bister K. [1983] Two unrelated cell-derived sequences in the genome of avian leukemia and carcinoma inducing retrovirus MH2. *EMBO J* 2(11): 1969–1975.

[18] Stéhelin D S. Saule. Roussel M. Sergeant A, Lagrou C. Rommens C. M. Raes B. [1983] Three New Types of Viral Oncogenes in Defective Avian Leukemia Viruses. I. Specific Nucleotide Sequences of Cellular Origin Correlate with Specific Transformation. *Cell* 34(3): 789-798.

[19] Chiswell D J. Ramsay G**.** Hayman M J. **[**1981] Two virus-specific rna species are present in cells transformed by defective leukemia virus OK10. *J Virol* 40(1): 301-304.

[20] Klempnauer K H. Bishop J M. [1984] Neoplastic transformation by E26 leukemia virus is mediated by a single protein containing domains of gag and myb genes. *J Virol* 50(1): 280–283.