

The Interacting Amino Acid of Envelope Protein

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Abstract – We measured the relative rates of amino acid change, as the ratio of the number of nonsynonymous to synonymous (silent) nucleotide substitutions, for six primate lentiviruses evolving in their respective hosts. These rates for the external envelope glycoprotein (gp120) and gag coding sequences are 2-3 times higher for pathogenic HIV-1 and SIVmac (macaque) than for minimally pathogenic SIVAGM and SIVsmm (sooty mangabey), and intermediate for HIV-2. A spectrum of pathogenicity has been observed for primate lentiviruses in their natural hosts. For example, human immunodeficiency virus type 1 (HIV-1) is a potent etiologic agent for AIDS in man, whereas there is no evidence to date which indicates that simian immunodeficiency virus from African green monkeys (SIVAGM) causes immunodeficiency in AGM. We speculate that the increased rates of nonsynonymous changes in gp120 and gag coding sequences are due to viral escape from immune surveillance and are indicative of higher immunogenicity of these proteins in their hosts. Based on these results and available experimental data, we conclude that there is a positive correlation between lentiviral pathogenicity and immunogenicity of the Env and Gag proteins in a given host. This hypothesis is consistent with recent data suggesting that immune system activation or autoimmunity induced by viral antigens may be important in the pathogenesis of AIDS *J Virol.* (1987).

Keywords – Interacting, Amino Acid, Envelope Protein, etc.

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INTRODUCTION

The amino acid groupings of the envelope protein buildings got from the nucleotide successions of seven AIDS virus disengages, three of which spoke to consecutive segregates from a similar patient. The present work is an expansion of recently distributed reports on the hereditary inconstancy of the envelope protein envelope protein complex, which predominantly centered around the DNA and essential amino acid groupings. By PC examination we anticipated the auxiliary structure of gp120 and gp41, the cleavage results of gp160, and anticipated potential antigenic destinations by superimposing this optional structure with the qualities for hydrophilicity, adaptability, surface likelihood, and glycosylation. Along these lines, 11 potential antigenic locales were distinguished, 9 of which were situated in the outside part (gp120) of the envelope protein and 2 in the layer bound bit (gp41). Five exceptionally factor areas were portrayed, all contained in gp120, agreeing with the anticipated epitopes. In consecutive detaches from a solitary patient, all modifications of auxiliary structures happened in those locales which were distinguished as antigenic epitopes. These outcomes demonstrate that genomic varieties of the AIDS virus appear to be showed for the most part in the extracellular segment

of the envelope protein. The way that those varieties correspond with conceivable antigenic destinations recommends that these areas might be immunogenic and might be of central significance for the pathobiology of the virus.

Amino Acid Structure and Properties

Proteins are one of the most abundant organic molecules and they play the largest range of roles in any macromolecule in the living world. Proteins may be structural, regulatory, contractile, protecting or contaminating, and may be used in packaging, storage, or membranes. They can also be contaminant or enzymes. Thousands of different proteins may contain cells of a living system, each for its own function. They have very different architectures as well as functions. They are all alpha amino acid polymers, though, which are organized in a linear sequence and connected by covalent links.

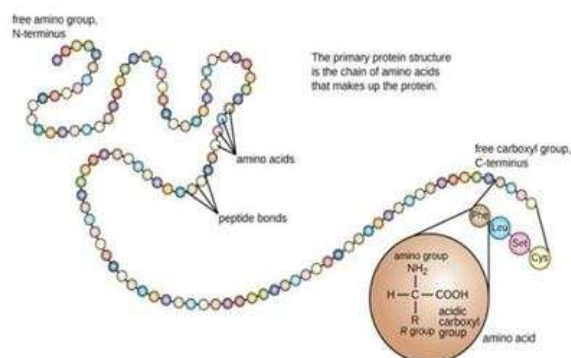
Formation of peptide bond and structure of primary protein

A large enzyme complex that contains a combination of RNA, proteins and protein, links proteins together in cellular systems. The name of

the complex is the ribosome. If the amino acids are combined to produce a specific protein, the genetic material found inside the messenger RNA (mRNA) molecule dictates the order in which they are arranged. The primary sequence of a protein is the order in which amino acids are arranged. In Chapter XX, the ribosome's translation process for synthesizing proteins will be explored in depth. This section will include only the chemical processes occurring during the synthesization of the following peptides/proteins and their physical properties. Dehydration (water loss) synthesis ties the primary series of protein together by combining the upstream amino acid carboxylic acid with the downstream amino acid amine function group to form an amide bond. Hydrolysis, on the other hand, necessitates the insertion of a water molecule in order to separate two amino acids and break the amide bond.

Protein Shape and its Function

The primary structure of each protein is characterized by its distinctive folding pattern. In short, the primary sequence of the amino acids in the protein chain is the sequential order. In the next chapter we will discuss protein folding, which results in the configurations of principal, tertiary and even quaternary protein.



Fibrous Proteins

The elongated protein structures are distinguished by fibrous proteins. This type of protein often consists of filaments or bundles that form structural fabrics in biological systems. The two most prevalent fibrous protein families are alpha-keratin and collagen in mammals.

1. *α-keratin*
2. *Collagen*

Globular Proteins

The spherical ("globe-like") protein is a spherical protein, and is one of the different forms of proteins. Global proteins are water-soluble, in contrast to fibrous or membrane proteins (forming in water colloids). There are several folding classes of globular proteins, since several different

architectures may fold into an approximately spherical form.

In particular, the word globin may apply to proteins, like globalin folding. The globin plating is a typical three-dimensional plating of proteins that distinguishes the superfamily globin-like protein. This fold normally comprises 8 alpha helices, although there are helix extensions in certain proteins. In the namesake families of the protein globin, hemoglobins, myoglobins, and phycocyanins, the globine fold is found. Myoglobin is, thus, the first protein fold found, as the composition of the first protein protein is resolved. The globin plug is called an all-alpha protein plug since it contains only helices.

Membrane Proteins

Proteins of the membrane are proteins which form part of biological membranes or interact with them. (1) integrated membrane proteins that are partially and/or permanently fixed to the membrane and (2) peripheral membrane proteins that are temporarily attached to the membrane by central or lipid bilayer proteins. Integrated membrane proteins are commonly called membrane proteins, or are monotonic integrated proteins that are attached to one side of their membrane.

Disordered Proteins

An IDP is a protein lacking a three-dimensional structure and is either set or organized. IDPs involve random bowls, pre-molten globules and massive multi-domain proteins that have been linked with modular connectors from completely unstructured to partly organized states. They are one of the most important protein groups (alongside globular, fibrous and membrane proteins).

LITERATURE REVIEW

Breakthrough the recent decades of widespread studies of Type 1 human immunodeficiency virus (HIV-1) we have had a great deal of evidence about the abillance capability and the cell contamination tool of each viral segment. HIV-1 is fifteen proteins and has one RNA. Among the two proteins, the start of cellular disease involves two glycoproteins (gp120 and gp41), formed by proteolytic cleavage of the precursor peptide gp160. The viral cell membrane fusion resulting from virus cell fusion by the transmembrayan envelope protein (gp41) responsible to produce the virus as the cell receptor (Gp120) is generally recognised as leading to a cell section. The three dimensional structure of the whole atom Gp41 (345 aminacids) is uncertain but non-covalent cooperation and its six single subunits generally supports the glycoprotein envelope (three Gp120

and 3 Gp41 subunits). There were two gem configurations of a small core protein of gp41. The core area is a community of six helices consisting of a snaked loop cutter of N36 on the inside and a C34 on the outside that is like a flu hemagglutinin adjustment of low pH, and Thus, the core sort is thus not the remaining Gp41 structure, but a fusion reaction structure. The proposed models of gp41 cell fusion were based on the framework for the core area and the key focus of recent research on gp41 cell fusion.

MOLECULAR DYNAMICS

Gp42 TM single-helix and trimeric helix strands are re-enacted utilising the Cray XD1 version of the GROMACS MPI from Huntsville's Alabama Supercomputer Centre (regularly running in equal on 4 Opteron processors). The helix was embedded into a single-helix strand or package of helix implanted in a hydrated lipid bilayer in the hydrated 1-palmetoyl-2-oloyl-sn-glycer-3-phatidylethanolamine (POPE). By forming a solvent seal, defining the hydrogen POPE around the helix, the helix was put in the fat bilayer. Hydration of the helix (or the helix bundle). The helix (or helix bundle) was introduced into the focus of the container in the opposite direction of a lipid bilayer plane. Dissolvable particles (lipid and agua) have been ejected because the isolation of the helix iota (or helix bundle) from each dissolved particle is not precisely the amount of the van der Waals radii of the two iotas. The structure was balanced for an all-inclusive period after vitality minimization, with positional constrained molecular dynamics (which dominated the helix bundle settings, however, enabled others to move) to match the thickness (or volume), weight and temperature (normally for around 3 ns).

AMINO ACIDS

Amino acids are natural aggravates that comprises of carboxyl just as an amino group. every amino acid have the alpha carbon attached to a hydrogen molecule, a 'R' group, carboxyl group and an amino group. The 'R' group shifts among amino acids and decides the contrasts between monomers of protein. There are 20 conventional amino acids, which are usually found in people. A buildup reaction, is subject for making the linkage between the amino acids. Peptide bond development is a buildup response prompting the polymerization of amino acids into peptides and proteins. Peptides are little chain comprising of a couple of amino acids. Various hormones and synapses are peptides. Moreover, a few anti-infection agents and antitumor specialists are peptides. Proteins are polypeptides of extraordinarily different length. The least difficult peptide, a dipeptide, contains a single peptide bond framed by the buildup of the carboxyl group of one amino acid with the amino group of the second with the disposal of going with water. (an) every amino

acid has its particular qualities characterized by the side chain 'R', which furnishes it with its specific job in a protein structure. In view of the penchant of the side chain to be in contact with polar dissolvable like water, amino acids might be arranged as hydrophobic (low affinity to be in contact with water), polar or charged (enthusiastically positive contact with water). Nevertheless, glycine, being one of the normal amino acids, doesn't have a side chain and hence it isn't easy to dole out it to any of these classes.

STRUCTURAL PROTEINS

The two viral envelope proteins, E and M, are C-terminal anchor series, category I integral membrane proteins. The E protein is mostly composed of β -sheets organised head-to-tail with the far end of every monomer incorporated into the lipid membrane through means of comparison with tick-borne encephalitis virus (Post et al., 1992; Lindenbach and Rice, 1999). The protein of E is composed of three structural domains and is both receptor-binding (haemagglutinin) to cell fusion events and have a pH dependence on acid. The second domain (domain III) comprises a fold characteristic of a constant field of immune globulin and the cell receptor is supposed to reflect this domain. At the edge of this domains of tick- and mosquitovirus, there is great overlap in the amino acid series. In domain III, certain mutations are equivalent to virulence modifications. A analysis is carried out in order to determine if a Domain II area could also be active in connecting the virus to receptors in monkey brains (Ni et al., 2000). Work on dengue virus E protein structure has increased considerably in recent years (see below); comparative studies can shed light on the details of the binding and replacement of amino acids with tropism in the tissue and attenuation of the yellow fever.

Envelope glycoprotein gp160

Oligomerates through mostly trimmings in the host endoplasmic reticulum. In a second time, gp160 transits the Golgi host, which completes glycosylation. The precursor is then proteolytically cut into the trans-Golgi and triggered to generate gp120 and gp41 by cell furine or furine-like proteases.

Surface protein gp120

Ties the virus to the lymphoid cell of the host by connecting to the main CD4 receptor. This association leads to the development of a high affinity binding site for a chemokine coreceptor such as CXCR4/CCR5. The ligand acts on both dendritic cell (DCs) and hepatic cells in liver sinus cells and sinus lymph nodes as a CD209/DC-SIGNR and CLEC4M/DC-SIGNR, respectively. These interactions facilitate the collection and

eventual transfer of viral particles to permissive cells at mucosal surfaces. The migration properties of dendritic cells in lymph nodes are subverted by HIV to access CD4+ T-cells.

Transmembrane protein gp41

It works as a viral protein in fusion type I. According to the new model, the protein contains a minimum of three conformational conditions; pre-fusion, pre-hairpin, and post-fusion, native hairpin. During fusion of viral and target intracellular membranes, the coiled coil regions (heptad repeats) assume a trimer-of-hairpins shape, placing the fusion peptide in near proximity to the C-terminal area of the ectodomain. The creation of this structure tends to drive apposition and eventual fusion of viral and target cell membranes. Complete fusion occurs in host cell endosomes and is dynamin-dependent, but some lipid transfer might occur at the plasma membrane. Long before the endosomal fusion, the virus undergoes clathrin based internalisation, limiting the surface exposure of conserved viral epitopes during fusion and reducing its effectiveness. Membranes fusion contributes to delivery of the nucleocapsid into the cytoplasm.

ENVELOPE PROTEIN Env and Vaccine Development

Recombinant protein subunit antibodies built up X4-tropic viral detaches depicted the original of envelope protein up-and-come immunization strategies. Until now, most recombinant envelope protein glycoproteins endorsed, as immunization competitors have been gp120 monomers, which summon frail counter acting agent reactions to homologous viruses and have not been effective at actuating antibodies ready to invalidate heterologous essential secludes at noteworthy titers. The counter acting agent answer plasmid DNA encoding gp120 improve with a recombinant gp120 protein subunit immunization bring out cellular and strong reaction, however the reaction was not beneficial. Utilization of existent weakend canarypox virus communicating ENVELOPE PROTEIN env and choke actuated answer against research center disconnects. DNA immunization techniques to date have predominantly brought about the commencement of low-titer neutralizer reactions, while plasmid DNA inoculation and various recombinant-vector based methodologies have been appeared to energize cellular invulnerable reactions against inside proteins. By screening of little atoms, The two drugs CD4-gp120 is known as viral fusion inhibitors, in particular NBD-556 and NBD-557.

- Envelope protein glycoprotein gp120 and gp41 proteins experience conformational changes to tie a Ligand.

- The key protein deposits which assume significant job for the official with gp120 with various inhibitors.
- A compound is dynamic or idle, or how its movement may be improved.
- Discover the adjustments in the coupling free vitality of a specific medication with envelope protein Env proteins. What instrument of opposition changes in the coupling free vitality of a specific medication with envelope protein env proteins?

OBJECTIVES OF THE STUDY

- To study on Antibody's function in Ligand stabilization
- To study on GP120-NBD14010 Dynamic MD Simulations
- To study on GP120 Double Hotspot Small-molecular binding
- To study on Binding of the CD4-Binding site NBD Analog Inhibitors
- To study on Binding the derivative receptor DMJ-II-121 to GP120

RESEARCH METHODOLOGY

Molecular simulation and modeling are undergoing drastic advancements. These are emerging as one of the most vital tools for fundamental and applied research in academia and industries in miscellaneous fields like drug-design and material science. Our science gains have been amplified and have greatly impacted on our society's development by theoretical and statistical methods used to prevent and deeply comprehend complicated scientific realities. There is currently no scientific field that does not use applied computer technology to further grasp and to study combined. Computer technology can be applied in analysing the molecular sequence, gene and non-coding regions can be understood, protein molecules estimated and essential features mapped, and comparative studies are conducted to explain dynamic biosphere biomolecular and numerous other facets of cellular and molecular physics. This chapter aims to provide essential background information regarding the theoretical and computational techniques used in the present investigation

Sample Size,

For the quantitative study the sample size is 5.

Sample Area

The data will be selected and analyzed Naya Raipur.

3.2 Molecular Modelling: A Potent Tool

Method of Molecular modelling is the technique of representing the molecular structures in the context of molecular and quantum mechanical equations. It describes three dimensional structural and conformational aspects of chemical structures. The molecular modelling is the method to study the phenomena of molecular structure, surface, dynamics and thermodynamics properties of inorganics, organics, polymers and materials. The molecular modelling technique is one of the best features used for description at atomic level or small group of atoms. This is in contrast to the electronic structure calculation, where electrons are considered explicitly. This method is very useful to study the complex system where many atoms or particles are taken during simulations.

3.3 Molecular Dynamic Simulation

Molecular dynamics (MD) simulation has been exploited in different types of biomolecular systems. These techniques are based on the experimental data derived from x-ray crystallography and NMR techniques. These techniques provide us structure, dynamics, thermodynamics parameters, comparative value of binding energy, binding affinity, mobility and stability of biological molecules like protein, DNA, carbohydrates, lipids etc, which are critical to biological function, that could not be acquired from static models. A brief description of MD simulation is presented here.

3.4 Methods for Free Energy Calculation

Free energy is an important thermodynamical parameters for biomolecules. The element Helmholtz (A) and the free energy function Gibbs is represented (G). Function A of Helmholtz is provided by

$$A = U - TS$$

Where U, S and T denote the internal energy, entropy and temperature of the system respectively. Since A is a perfectly differential quantity, then

$$dA = TdS - PdV - TdS - SdT \quad (\because dU = TdS - PdV)$$

$$\text{or, } dA = -PdV - SdT$$

DV and dT would be zero for NVT ensemble, therefore dA=0. Consequently, free energy from Helmholtz is suitable to NVT ensemble.

In a similar way, Gibbs free energy is mathematically given as:

$$G = H - TS$$

where H (=U + PV) is the enthalpy of the system. Like Helmholtz function, G is also exactly differential quantity. Hence, we finally get

$$dG = VdP - TdS$$

At constant temperature and pressure, dG=0. Hence 'G' is an appropriate function to deal with NPT ensemble.

3.5 MM-PB (GB)/SA Method

In order to quantify ligand free energy, MM-PBSA and MMGBSA methods are used with a recipient in forming a protein ligand complex where protein is used as a receptor. The following method refers to the contribution of GP, the disparity in energy attributed to translational and rotational motion, solvation energy and entropy contributions:

$$G = G + G_{\text{trans/rot}} + G_{\text{sol}} - TS_{\text{tot}}$$

where RHS is the first concept of contribution for the gas process, which is the amount of the energy of electrostatics, van der Waals and internal energy i.e.

$$G_{\text{gas}} = E_{\text{ele}} + E_{\text{vdw}} + E_{\text{int}}$$

The second term of the RHS in equation (2.16) is the energy arising due to translational/rotational motion. This term is equal to 3RT in classical mechanics which is generally neglected in MMPB/SA calculations. The solvation energy consists of non-polar and polar solvation terms. The entropy term based on the degree of freedom of molecule in terms of translational, rotational and vibrational motions.

Theoretically, the ligand, protein and complex equation are important. The resulting free binding energy is:

$$\Delta G = G_{\text{comp}} - (G_{\text{lig}} + G_{\text{protein}})$$

Equation (2.18) has been explained as under:

Unbound ligand free energy: The free energy for the inhibitors is given by

$$G(L) = E_{\text{gas}}(L^u) + G_{\text{sol}}(L^u) - TS_{\text{ideal}}(L^u)$$

'u' points the unbound conformation of the ligand.

Unbound protein free energy: During the simulation of unbound protein the classical mechanic methods are used. Its free electricity

includes complete intra-molecular capacity, E_{gas} and entropy inputs, solvation-free, TS_{ideal}.

$$G(P) = E_{\text{gas}}(P^u) + G_{\text{sol}}(P^u) - TS_{\text{ideal}}(P^u)$$

Complex free energy: Both MM and QM approaches may be used for the complex. It consists of the combined amount of energy conditions for the protein and ligand and the expression for the relationship between the protein and the ligand (P/L). The complex's free electricity has the following terms:

$$G(C) = E_{\text{gas}}(P^b) + E_{\text{gas}}(L^b) + G_{\text{sol}}(C^b) - TS_{\text{ideal}}$$

The number of Ebond, E_{coul} and E_{vdw} is decomposed where. The superscript b marks the binding shape.

The non-covalent combination of two molecules may be composed of the binding free energy

$$\Delta G_{\text{bind}} = \Delta G(L + P - C) = G(C) - G(L) - G(P)$$

$$\text{or, } \Delta G_{\text{bind}} = \Delta E_{\text{int}} + \Delta G_{\text{solv}} - T\Delta S_{\text{ideal}} + \alpha \Delta E_{\text{vdw}}(P/L)$$

$$\text{where, } \Delta E_{\text{int}} = E_{\text{int}}(P^b) - E_{\text{int}}(P^u);$$

$$\Delta G_{\text{solv}} = G_{\text{solv}}(C^b) - G_{\text{solv}}(L^u) - G_{\text{solv}}(P^u)$$

$$\text{and } -T\Delta S_{\text{ideal}} = -TS_{\text{ideal}} + TS_{\text{ideal}}(L^u) + TS_{\text{ideal}}(P^u)$$

The empirical scaling factor α is taken to balance the van der Waals energy relative to the electrostatic energy. Here, The empirical scaling factor α is taken as fitting parameter, which is outcome of experimental results. E_{int} (change in protein intramolecular energy) is calculated by using MMGBSA method. ΔG_{solv} is composed of Nonpolar contribution and polar contribution [18]. Nonpolar solvation energy accounts for the unfavorable cavity formation and favorable van der Waals interaction between solute atoms and the solvent [19].

$$E_{\text{solv,np}} = \gamma \cdot A + b$$

If A means the Open Surface of the Solvent (SASA), β and b are analytical constants that could have different values. The linear Poisson Boltzmann (PB) [20] equation is used in the calculation of polar solvation capacity, relating charges mass, $\phi(r)$, electrostatic potency, oscillation, oscillating (r), in nonuniform dielectric allowable media, oscillating (r), for the solvent 80 and 1 respectively and for the solution

$$\Delta \epsilon(r) \Delta \phi(r) = -4\pi \rho(r) + \kappa^2 \epsilon(r) \Delta \phi(r)$$

Where μ is the screening parameter Debye-Huckel to take the electrostatic screening effect into consideration. A major thermodynamic parameter, known as entropy (ETE), has developed in the

protein-ligand system changes in translation, rotation and vibrational degrees of freedom. Further, this entropy terms due to loss of degree of freedom upon association, is decomposed into translational (S_{trans}), rotational (S_{rot}) and vibrational (S_{vib}) contributions which can be calculated using standard equations of statistical mechanics.

CONCLUSION

The advances in double dynamic medications might be useful for affordable and toxicological viewpoints albeit significant buildups are dynamic in protein Ligand buildings, they don't outfit physical information for the unmistakable quality in connection pair of every buildup. Consequently, it gets compulsory to explain the physical movement of wonder at the degree of nuclear goals, in order to twofold checks the physical action of all deposits close to the connection site taking an interest in adjustment of the complex. Here we utilized computational strategies to research collaboration among gp120 and ligands utilizing MD reenactment techniques. Our discoveries elevate us to approve the thermodynamic outcome. Likewise, this examination shows that the technique utilized will able to mimic the trial approval of the consequence of restricting free energies. While the development of antiretroviral therapy has slowed down the trend of global spread of the disease, the continued emergence of mutated strains has accentuated the need of new therapeutically strategy. Epidemiological and evolutionary studies are necessary to track and identify the trend of mutation rate of the virus in different geographical areas and occurrence of different viral strains. Likewise, it is necessary to understand the biology of virus in terms of the role of viral proteins within the cell as well as their interaction with cellular factors in order to develop suitable therapeutic regimen. In this thesis I have studied the role of HIV-1 gag and vpu and how a point mutation in Gag matrix region and a mutation in vpu start codon affect virus replication, infectivity and Envelope incorporation in lab adapted cell lines as well as primary cells which represents natural target of HIV-1.

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