Infection, Genetics and Evolution 92 (2021) 104837

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid

Research paper

In silico analysis of molecular interactions between HIV-1 glycoprotein gp120 and TNF receptors

Neyla Maria Pereira Alves [a,*], Ronald Rodrigues de Moura [b], Lucas Coêlho Bernardo [a,c], Almerinda Agrelli [a,c,e], Ana Sofia Lima Estevão de Oliveira [c], Natália Pereira da Silva [a], Sergio Crovella [d], Lucas André Cavalcanti Brandão [a,c]

[a] Department of Pathology, Federal University of Pernambuco, Recife, Pernambuco, Brazil
[b] Department of Advanced Diagnostics, IRCCS Materno Infantile Burlo Garofolo, Trieste, Friuli Venezia Giulia, Italy
[c] Laboratory of Immunopathology Keizo Asami (LIKA), Federal University of Pernambuco, Recife, Pernambuco, Brazil
[d] Department of Biological and Environmental Sciences, College of Arts and Sciences, University of Qatar, P.O. Box 2713, Doha, Qatar
[e] Laboratory of Advanced Nanomaterials (LANO), Center for Strategic Technologies Northeastern (CETENE), Recife, Pernambuco, Brazil

ARTICLE INFO

Keywords:
Immunological pathway
gp120 modulation
HIV-1 infection
Molecular dynamics
Molecular docking

ABSTRACT

Proinflammatory microenvironmental is crucial for the Human Immunodeficiency Virus Type 1 (HIV-1) pathogenesis. The viral glycoprotein 120 (gp120) must interact with the CD4+ T cell chemokine receptor (CCR5) and a co-receptor C-X-C chemokine receptor type 4 (CXCR4) to let the virus entry into the host cells. However, the interaction of the viral particle with other cell surface receptors is mandatory for its attachment and subsequently entry. Tumor Necrosis Factor receptor type I (TNFR1), type II (TNFR2) and Fas are a superfamily of transmembrane proteins involved in canonical inflammatory pathway and cell death by apoptosis as responses against viral pathogens. In our study, we performed an *in silico* evaluation of the molecular interactions between viral protein gp120 and TNF receptors (TNFR1, TNFR2 and Fas). Protein structures were retrieved from Protein Databank (PDB), and Molecular Docking and dynamics were performed using ClusPro 2.0 server and GROMACS software, respectively. We observed that gp120 is able to bind TNFR1, TNFR2 and Fas receptors, although only the TNFR2-gp120 complex demonstrated to produce a stable and durable binding. Our findings suggest that gp120 may act as an agonist to TNF-α and also function as an attachment factor in HIV-1 entry process. These molecular interaction by gp120 may be the key to HIV-1 immunopathogenesis. In conclusion, gp120 may stimulate pro-inflammatory and apoptotic signaling transduction pathways mediated by TNFR2 and may act as an attachment factor retaining HIV-1 viral particles on the host cell surface.

1. Introduction

The main outcome in Human Immunodeficiency Virus (HIV) pathogenesis is the CD4+ T lymphocytes depletion, which culminates with Acquired Immunodeficiency Syndrome (AIDS). The whole mechanisms of CD4+ cell loss is complex and multifactorial, remaining a controversial subject. In fact, unveil interactions between cell host and HIV viral particle may play an important role in the HIV infection and in AIDS physiopathology (Chorin et al., 2014; Garg and Joshi, 2017; Herbein et al., 2010).

In the HIV type 1 (HIV-1) pathogenesis, a persistent proinflammatory microenvironmental and apoptotic mechanisms are important for the mechanism of viral latency (Kruize and Kootstra, 2019), which is crucial for the onset of chronic infection (Li et al., 2019). The main mechanism reported to be involved in CD4+ T-cell loss is the "tap-and-drain" model that considers that the destruction of the CD4+ T cells (the drain) during the chronic phase of HIV-1 infection is superior to the homeostatic production (the tap) of these cells (Sedaghat et al., 2008).

To entry CD4+ cells, HIV-1 envelope glycoprotein gp120 interacts with the host cell membrane proteins CCR5 and CXCR4 (Berger and

* Corresponding author at: Department of Pathology, Federal University of Pernambuco, Av. Prof. Moraes Rego, S/N, Cidade Universitária – CEP, 50670-901 Recife, Pernambuco, Brazil.
E-mail addresses: neyla.alves@ufpe.br (N.M.P. Alves), ronaldmoura1989@gmail.com (R.R. de Moura), lucascoelhobernardo.lb@gmail.com (L.C. Bernardo), almerindaapimentel@gmail.com (A. Agrelli), anasofialima2@hotmail.com (A.S.L.E. de Oliveira), natalia.ciac.ns@gmail.com (N.P. da Silva), crovelser@gmail.com (S. Crovella), lucabrand@gmail.com (L.A.C. Brandão).

https://doi.org/10.1016/j.meegid.2021.104837
Received 10 February 2021; Received in revised form 17 March 2021; Accepted 30 March 2021
Available online 1 April 2021

Alkhatib, 2007; Yoon et al., 2010); however, during HIV-1 attachment, gp120 also interacts with other cell surface receptors (Clapham and McKnight, 2001). It is important to differentiate entry receptors from attachment factors. Entry receptors are interactions that result viral uptake, while attachment factors are interactions that will only retain viral particles on cell surface (Agrelli et al., 2019).

Apoptosis has been related as an important mechanism for CD4+ depletion during HIV infections since 1990s (Pitrak et al., 2014). Moreover, gp120 is reported to induce the expression of Fas and TNF receptors in CD4+ and CD8+ T lymphocytes, resulting in the production of proinflammatory cytokines, such as Tumor Necrosis Factor α (TNF- α) (Herbein et al., 2010).

Tumor Necrosis Factor receptors (TNFR) are a superfamily of transmembrane proteins involved in immunological responses against pathogens. TNFR type I (TNFR1), TNFR type 2 (TNFR2) and Fas are the main proteins involved in canonical inflammatory pathway and cell death by apoptosis. Both TNFR1 and TNFR2 are activated by endogenous ligand TNF-α (Atretkhany et al., 2020; Yang et al., 2018).

Fas and TNFR1/2 are proteins belonging to the tumor necrosis factor receptor (TNFR) superfamily. These proteins contain an intracellular and an extracellular domain, which are responsible for the activation of the signaling pathway and the ligand binding, respectively. Fas and TNFR1 are death receptors with a protein interaction module called the death domain (DD) in their intracellular region that mediates ligand-induced cell death (Li et al., 2013). On the contrary, TNFR2 is an activating receptor that does not contain DD and its activation directly recruits the TRAF1 or TRAF2/cIAP1–2 complexes (Atretkhany et al., 2020; Yang et al., 2018), regulating the activation of nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways (Cox and Canzian, 2001; Li et al., 2013). Fas ligand (FasL) binds to Fas and activates apoptotic mechanisms similar to those induced by TNF-α *via* TNFR1, which is another possible pathway for apoptosis induction in HIV-1 infected cells (Mbita et al., 2014).

Furthermore, TNFR1 and TNFR2 present in their extracellular portion cysteine-rich domains (CRD) with multiple disulfide bonds and a preserved region called pre-ligand assembly domain (PLAD), both located in the N-terminal region (CRD1), that is critical for assembly of functional receptor complexes on the cell surface, and a ligand-binding domain for ligand-receptor signaling (Atretkhany et al., 2020; Mukai et al., 2013; Steeland et al., 2018). TNF-α exists as a cone-shaped homotrimer (chains A, B and C) in two forms: a trimeric membrane-bound ligand and a soluble trimeric molecule. Each monomer consists of two packed antiparallel β-sheets in a "jelly-roll" conformation (eight β-strands arranged in two four-stranded sheets) with an outer leaf (N-terminal) (the surface of the trimer) containing hydrophilic residues and a hydrophobic inner leaf (C-terminal) which is involved in trimer contacts (Eck and Sprang, 1989; Idriss and Naismith, 2000). In this context, *in silico* approaches are examples of current computational methods have used to complement experimental analyzes and aid in the construction of biological structural interactions.

Several intra- and extracellular mechanisms are involved in apoptotic and inflammatory processes, although little is known about the role of gp120 on the activation of TNFR1/2 and Fas receptors. Here, we investigated *in silico* the molecular interactions between HIV-1 gp120 protein and the TNF receptors (TNFR1, TNFR2 and Fas).

2. Materials and methods

2.1. Proteins structures

Protein structures were retrieved from Protein Databank (PDB) (Berman et al., 2000) based on their resolutions. The following protein structures were used: Transmembrane TNF-α (PDB ID: 1TNF); TNFR1 (PDB ID: 1EXT); TNFR2 (PDB ID: 3ALQ); Fas (PDB ID: 3THM); FasL (PDB ID: 4MSV); and gp120 (PDB ID: 4RZ8). Water and others molecules and ions were removed of the structures using Chimera v. 1.13.1 software (Pettersen et al., 2004).

2.2. Protein-protein docking and molecular dynamics simulations

ClusPro server (Kozakov et al., 2017) was used to perform molecular docking, choosing the models with the lowest cluster score. TNF-α was used as native ligand of TNFR1 and TNFR2. FasL was used as reference ligand for Fas. Gp120 was used as test ligand with TNFR1, TNFR2 and Fas.

The complexes from the docking simulations were further investigated by molecular dynamics (MD) simulations, which were performed with GROMACS software (version 2018.3) (Abraham et al., 2015).The force field used for all simulations was GROMOS/53A6. The tridimensional structures were solvated into a 0.7 nm cubic box with SPC/E water molecules and then neutralized by adding Na^+ or Cl^- ions, according with the demand. The temperature and pression were adjusted to 310 K and 1 bar, and simulations were carried out for 100 ns. The covalent bonds were constrained using LINCS (Linear Constraint Solver) algorithm (Möhle et al., 1997), whereas the electrostatic interactions were assessed through the PME (Particle Mesh Ewald) method (Darden et al., 1993). The MD trajectories were recorded every 10 ps.

To evaluate the stability of the complexes, we considered the root mean squared deviation (RMSD), the radius of gyration (Rg) and the solvent-accessible surface area (SASA) along the simulations.

2.3. Hydrogen bonds

The molecular interactions (hydrogen bonds) between endogenous ligands and tested ligands (TNF and gp120, respectively) with TNFR2 receptor were predicted using LIGPLOT v.4.5.3 (Wallace et al., 1995).

3. Results

Docking results are demonstrated in Table 1. TNF-α and FasL binds into the active-binding region of TNFR1/2 and Fas extracellular domains, respectively. Gp120 binds TNFR2 at the same region that TNF-α, although with less affinity (cluster scores: −951.3 and − 1831.9, respectively). Moreover, gp120 did not bind with TNFR1 or Fas on regions that TNF-α and FasL binds, respectively, suggesting the specificity of gp120 for TNFR2 (Fig. 1).

MD simulations showed that the bindings between endogenous ligands (TNF-α and FasL) and their respective receptors (TNFR1/2 and Fas) were more stable than the bindings between gp120 and TNFR1 or Fas along the simulations (Fig. 2). However, the TNFR2-gp120 complex demonstrated stability (Fig. 3A), although one unit of the TNFR2 trimmer dissociated from the complex and reintegrated close to 100 ns. Furthermore, although RMSD, Rg and SASA plots from the Fas-gp120 complex indicates a stable system (Supplementary material), the region gp120 binds does not match the Fas active-binding region,

Table 1
Molecular Docking results of the interactions between the analyzed receptors (TNFR1, TNFR2 and Fas) and the ligands (gp120, TNF-α and FasL).

Receptor	Ligand	Cluster value	Presence of interaction
TNFR1	TNF-α	−1300,7	Yes
TNFR1	gp120	−888,6	No
TNFR2	TNF-α	−1831,9	Yes
TNFR2	gp120	−951,3	Yes
Fas	FasL	−970,9	Yes
Fas	gp120	−932,6	No

TNFR1 – TNF receptor superfamily member 1A; TNFR2 – receptor superfamily member 1B; Fas – Fas cell surface death receptor; TNF-α – tumor necrosis factor alpha; gp120 – HIV-1 envelope glycoprotein; FasL – Fas ligand. The presence of interaction was determined based on joint of reference ligand (native) or test ligand at the active-binding regions of the evaluated receptors in molecular docking simulations.

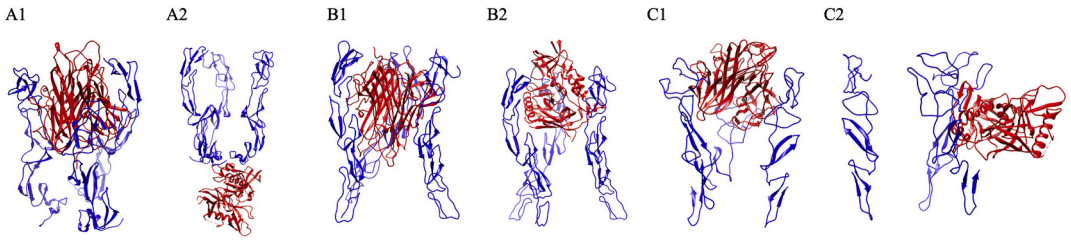

Fig. 1. Receptor-ligand complexes: TNFR1-TNF-α (A1), TNFR1-gp120 (A2), TNFR2-TNF-α (B1), TNFR2-gp120 (B2), Fas-FasL (C1) and Fas-gp120 (C2). Gp120 binds the same active-binding region that TNF-α in the TNFR2.

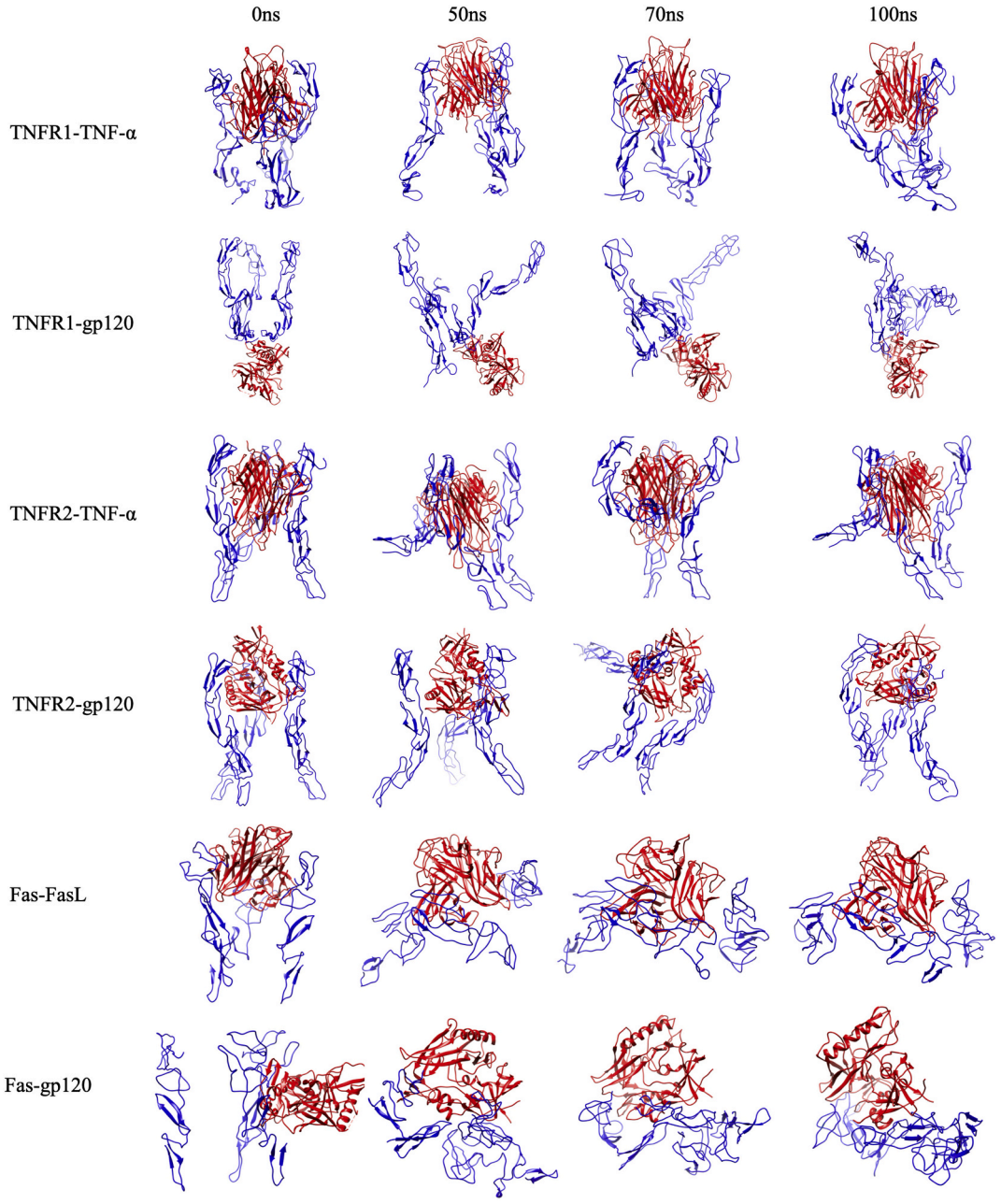

Fig. 2. Interactions of the receptors (in blue) and ligands (in red) at 0 ns (initial time), 50 ns, 70 ns and 100 ns (final time). TNFR2 receptor and TNF-α have showed to have a stable bond. Gp120 is able to bind in the same active-binding region that TNF-α in the TNFR2, but not TNFR1 or Fas. At 50 ns and 70 ns, the TNFR2-gp120 complex shows a discrete dissociation of one of the TNFR2 trimers. At 100 ns occurs the restoration of the TNFR2 trimer to the complex.

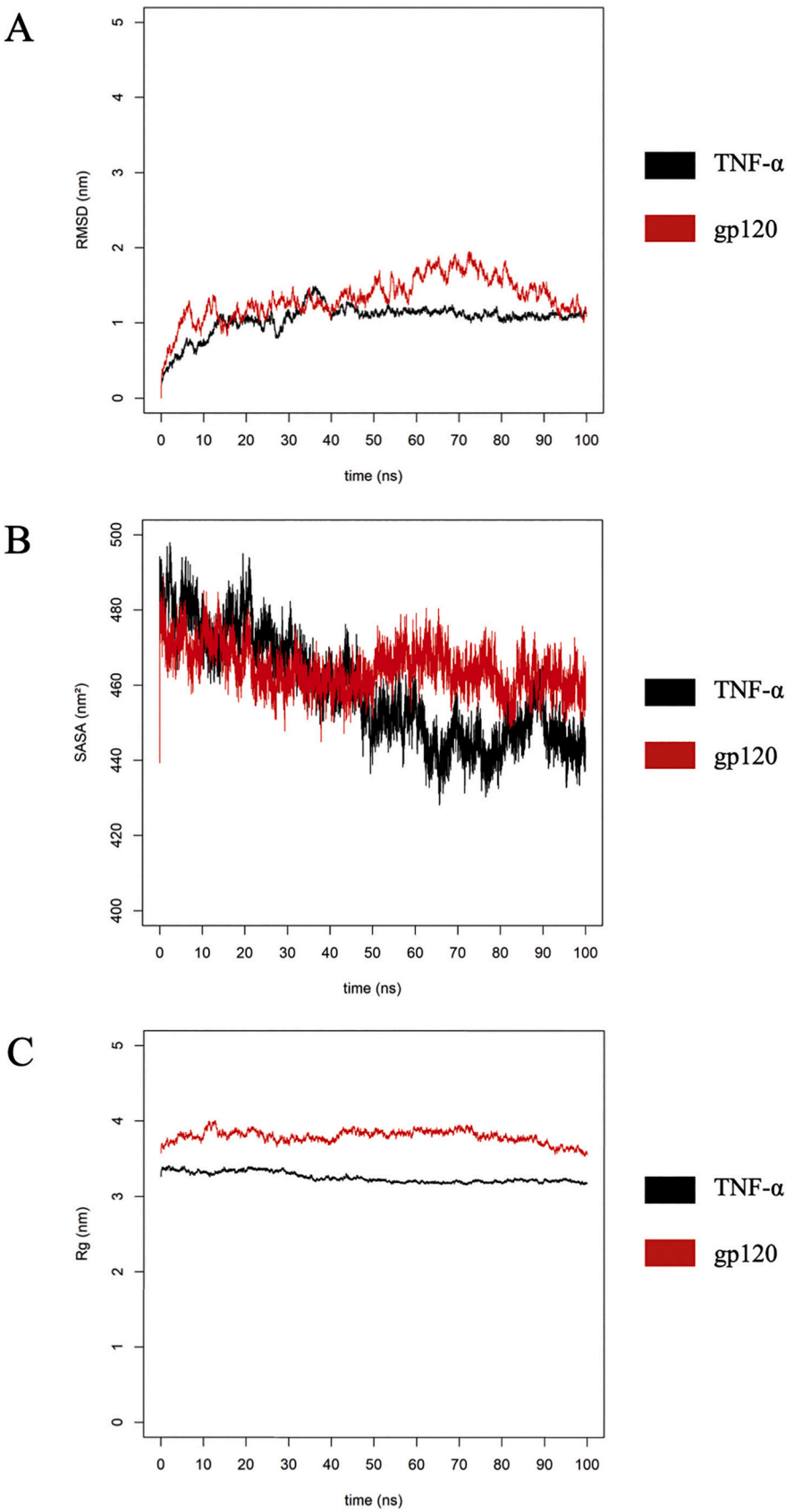

Fig. 3. Molecular dynamics analysis of TNF-α (in black) and gp120 (in red) ligands with TNFR2. The root mean square deviation (RMSD) (A) indicated that the binding between TNF-α and TNFR2 is more stable. Approximated values of solvent accessible surface (B) (SASA) were observed in both simulations. Radius of gyration (Rg) (C) indicates an enhancement in the stability of the TNF-α (after 50 ns) and gp120 (between 50 ns and 70 ns) ligands through time.

suggesting that the binding is not able to activate the receptor.

TNF-α and gp120 maintained structure compaction throughout the simulation in complex with TNFR2 (Fig. 3B). TNFR2-gp120 complex remained stable between 50 ns and 70 ns, while TNFR2-TNF-α remained stable from 50 ns until 100 ns (Fig. 3C). This result corroborates with the RMSD values, indicating greater stability between TNFR2-TNF-α (1 nm) complex.

LigPlot results of the analyzed complexes (TNFR2-TNF-α and TNFR2-gp120) is demonstrated in Table 2. Three hydrogen bonds were formed between Alanine, Arginine and Tyrosine residues (in the TNF-α chains) with T, S and R chains of the TNFR2, whereas Serine, Alanine, Glycine, Asparagine and Aspartate residues in the chain A of gp120 interacted with residues in the R and S chains of the TNFR2. Both TNF-α and gp120 ligands formed hydrogen bonds in the same residues (Thr27, Ser73 and Arg113) in the TNFR2 chains.

In the TNFR2, the hydrogen bond in the Thr27 residue was shorter in length when formed with TNF-α than with gp120, while Ser73 was shorter with Ser365 (in the chain A of gp120) than with Ala33 (in the A chain of TNF-α). Arg113 residue (in three chains of the TNFR2) exhibited interactions with both ligands. Residue Arg113 (in the TNFR2) formed more hydrogen bonds with gp120 than with TNF-α (Fig. 4).

4. Discussion

We found that gp120 is able to bind TNFR1, TNFR2 and Fas death receptors. However, only TNFR2-gp120 complex demonstrated to produce a stable and durable binding (cluster value: -951,3; RMSD: 1–2 nm). In addition, our results suggest that gp120 forms a strong bond with chains S and T of TNFR2.

Oligomerization of TNF receptors is necessary for stability of the receptor-ligand and it regulates the inflammation, proliferation and apoptosis intracellular signaling processes (Su and Wu, 2020). TNFR2 exhibits four CRD domains on regions of cell surface, two of which (CRD2 and 3) are denominated TNF-α-binding domains, triggering intracellular signalization (Mukai et al., 2013). TNFR2 presents three basic amino acids at its binding interface: Arg77, Lys108 and Arg133; TNF-α interacts with TNFR2 through Asp143, Gln 149 and Glu23 by hydrogen bonds (Mukai et al., 2013). Notably, the residues involved in the TNF-α binding are located in the CRD2 domain of TNFR1 (Arg77) and in the CRD3 domain of TNFR2 (Arg113) (Mukai et al., 2013). Our findings suggest that HIV-1 glycoprotein gp120 is able to compete TNFR2 endogenous ligand (TNF-α) for the binding sites, and may act as an agonist, once residues Gly324, Asn301 and Asp440 in gp120 formed hydrogen bonds with the residue Arg113 in the TNFR2. Considering the TNFR2 activation possibly regulates cell signaling and induce the recruitment of adapter proteins, mainly TNFR-associated factor (TRAF)2 (Yoon et al., 2010), it may stimulate signal transduction associated to cell proliferation, survival and/or maintenance of T_{reg} compartment (Mukai et al., 2013).

In the canonical pathway of inflammation, activation of TNFR2 transduces signal through receptor-associated cytoplasmic proteins, such as TRAF1 and TRAF2 (Atretkhany et al., 2020). Then, TRAF1/2 phosphorylates phosphoinositide 3-kinase (PI3K) in the cytoplasm, which culminates with the increase of chemokines, interleukins (IL-2, IL-6, IL-8, and IL-18) and cyclooxygenase 2 COX-2 expression (Kumar et al., 2013). PI3K activates protein kinase B (Akt) leading to the activation of the nuclear transcription factors, such as NF-κB and STAT5. NF-κB pathways are associated with transcription genes (such as interferon regulatory factor (IRF)1 and STAT1) and cell survival and proliferation in macrophages (Wajant and Siegmund, 2019). STAT5 can act on expression of the transforming growth factor (TGF)-β and IL-10 genes in T_{reg} cells (Yang et al., 2018). Furthermore, TRAF2 signal transduction can also activate the MAPK/JNK pathway and induce the production of pro-apoptotic proteins in these cells. A study reported that HIV-1 have the capacity to increase MAPK/JNK signaling pathway by gp120, Tat and Nef viral proteins (Gong et al., 2011); in this context, according to our results, gp120 may trigger pathways mediated by TNFR2, such as pro-inflammatory and apoptotic. Previous studies have shown that gp120 is involved with the stimulation and early production of IL-10 and IL-12 in monocytes/macrophages during HIV-1 infection (Gessani et al., 1997) and that gp120 is implicated in oxidative stress, disruption of mitochondrial membrane potential and apoptosis in HIV disease (A Perl and Banki, 2000).

Our results suggest that gp120 may be exploited by HIV-1 as an attachment factor. Currently, it is known that HIV-1 uses cell surface constituents such as heparan sulfate (Vivès et al., 2005), lectin-like receptor Siglec-1 (CD169) (Ruffin et al., 2019), and galectin-1 (Ouellet et al., 2005) for attachment and concentration at the cell surface. It should be noted that the number and the location of glycosylation sites in gp120 is a key factor for entry (Tian et al., 2016). Moreover, we believe that understanding the HIV-1 molecular interactions may favor future studies involving cell depletion and/or incomplete immune recovery as well as blocking entry factors in the HIV-1 infections.

Table 2
Hydrogen bonds formed among residues in the TNFR2 receptor (chains T, R, S) and the respective residues in the ligands TNF-α and gp120.

Complex	TNFR2 (chain)	Ligand (chain)	Length (Å)
TNFR2-TNF-α	Ser73 (T)	Ala33 (A)	3.3
	Thr27 (S)	Arg6 (B)	1.93
	Arg113 (R)	Tyr115 (C)	2.78
TNFR2-gp120	Ser73 (T)	Ser365 (A)	2.95
	Arg113 (T)	Ala145 (A)	2.5
	Thr27 (S)	Ser110 (A)	2.73
	Arg113 (S)	Gly324 (A)	2.77–2.79
	Arg113 (S)	Asn301 (A)	2.66
	Arg113 (S)	Asp440 (A)	2.74–2.75

Ser – serine; Thr – threonine; Arg – arginine; Ala – alanine; Tyr – tyrosine; Gly – glycine; Asn – asparagine; Asp – aspartate.

5. Conclusions

We concluded that gp120 was unable to induce extrinsic apoptosis pathway mediated by TNFR1 or Fas, although may act as an agonist to TNF-α considering ligand-induced pathways mediated by TNFR2 during HIV-1 infection. In this context, we hypothesized that the cytokines involved in these mechanisms could to attract more immunological cells, create an inflammatory microenvironment and contribute for the formation of HIV-1 reservoirs in infected cells. In addition, our results suggest that gp120 may also act as an attachment factor, corroborating for HIV-1 viral particle fixation on the host cell. Further *in vitro* and *in vivo* assays that investigates these interactions are needed.

Declarations of Competing Interest

None.

Ethics approval and consent to participate

We wish to confirm that there are no known conflicts of interest associated with this publication.

Consent for publication

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have

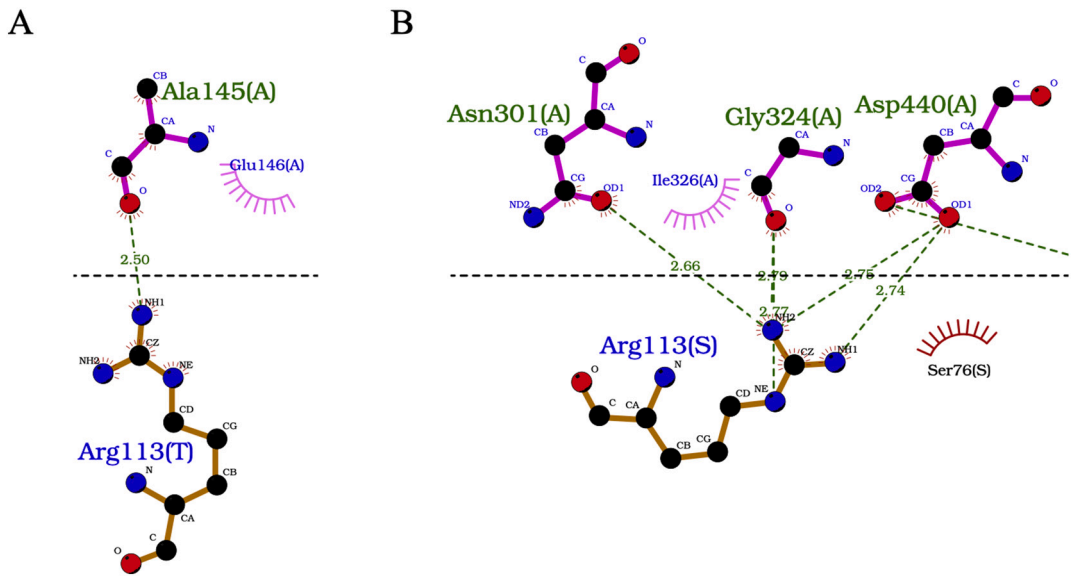

Fig. 4. Hydrogen bonds between residues in the TNFR2-TNF-α and TNFR2-gp120 complexes: (A) Arg113 residue in the TNFR2 T chain binds to the Ala145 residue in the TNF-α ligand with 2.5 Å length; (B) Arg113 residue in the TNFR2 S chain binds to the Asn30, Gly324 and Asp440 residues of the gp120 ligand with 2.66, 2.77–2.79 and 2.74–2.75 Å length, respectively.

followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding author and which has been configured to accept email from neyla.alves@ufpe.br.

Authors' contribution

1. Study Design: Neyla Maria Pereira Alves, Ronald Rodrigues de Moura, Lucas André Cavalcanti Brandão.
2. Data Collection: Ronald Rodrigues de Moura, Lucas C. Bernardo, Almerinda Agrelli, Natália Pereira da Silva, Ana Sofia Lima Estevão de Oliveira.
3. Data interpretation: Neyla Maria Pereira Alves, Ronald Rodrigues de Moura, Lucas C. Bernardo, Almerinda Agrelli.
4. *In silico* Simulations: Ronald Rodrigues de Moura, Natália Pereira da Silva.
5. Curation: Lucas C. Bernardo, Almerinda Agrelli, Ana Sofia Lima Estevão de Oliveira, Sergio Crovella.
6. Manuscript Preparation: Neyla Maria Pereira Alves, Almerinda Agrelli, Sergio Crovella, Lucas André Cavalcanti Brandão.
7. Literature Search: Neyla Maria Pereira Alves, Lucas C. Bernardo, Almerinda Agrelli, Ana Sofia Lima Estevão de Oliveira.

Funding

We acknowledge the financial support by the National Council for the Improvement of Higher Education – Brazil (CAPES) and the National Council for Scientific and Technological Development – Brazil (CNPq).

Acknowlegments

We acknowledge the financial support by the National Council for the Improvement of Higher Education – Brazil (CAPES) and the National Council for Scientific and Technological Development – Brazil (CNPq).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.meegid.2021.104837.

References

Abraham, M.J., Murtola, T., Schulz, R., Páll, S., Smith, J.C., Hess, B., Lindah, E., 2015. Gromacs: high performance molecular simulations through multi-level parallelism from laptops to supercomputers. SoftwareX 1–2, 19–25. https://doi.org/10.1016/j.softx.2015.06.001.

Agrelli, A., de Moura, R.R., Crovella, S., Brandão, L.A.C., 2019. ZIKA virus entry mechanisms in human cells. Infect. Genet. Evol. 69, 22–29. https://doi.org/10.1016/j.meegid.2019.01.018.

Atretkhany, K.N., Gogoleva, V.S., Drutskaya, M.S., Nedospasov, S.A., 2020. Distinct modes of TNF signaling through its two receptors in health and disease. J. Leukoc. Biol. 1–13 https://doi.org/10.1002/jlb.2mr0120-510r.

Berger, E.A., Alkhatib, Ghalib, 2007. HIV gp120 interactions with coreceptors: insights from studies with CCR5-based peptides. Eur. J. Med. Res. 12, 403–407.

Berman, H.M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T.N., Weissig, H., Shindyalov, I.N., Bourne, P.E., 2000. The protein data bank. Nucleic Acids Res. 28, 235–242. https://doi.org/10.1093/nar/28.1.235.

Chorin, E., Gal-Garber, O., Yagel, Y., Turner, D., Avidor, B., Berke, G., Hassin, D., 2014. PBMC of HIV-infected patients contain CD8 T cells that form conjugates with and kill HIV- infected autologous CD4 T cells. Immunology 30. https://doi.org/10.1111/imm.12385.

Clapham, P.R., McKnight, Á., 2001. HIV-1 receptors and cell tropism. Br. Med. Bull. 58, 43–59. https://doi.org/10.1093/bmb/58.1.43.

Cox, D.G., Canzian, F., 2001. Genotype transposer: automated genotype manipulation for linkage disequilibrium analysis. Bioinformatics 17, 738–739. https://doi.org/10.1093/bioinformatics/17.8.738.

Darden, T., York, D., Pedersen, L., 1993. Particle mesh Ewald: an N·log(N) method for Ewald sums in large systems. J. Chem. Phys. 98, 10089–10092. https://doi.org/10.1063/1.464397.

Eck, M.J., Sprang, S.R., 1989. The structure of tumor necrosis factor-α at 2.6 Å resolution. Implications for receptor binding. J. Biol. Chem. 264, 17595–17605. https://doi.org/10.2210/pdb1tnf/pdb.

Garg, H., Joshi, A., 2017. Host and viral factors in HIV-mediated bystander apoptosis. Viruses 9, 1–23. https://doi.org/10.3390/v9080237.

Gessani, S., Borghi, P., Fantuzzi, L., Varano, B., Conti, L., Puddu, P., Belardelli, F., 1997. Induction of cytokines by HIV-1 and its gp120 protein in human peripheral blood monocyte/macrophages and modulation of cytokine response during differentiation. J. Leukoc. Biol. 62, 49–53. https://doi.org/10.1002/jlb.62.1.49.

Gong, J., Shen, X.H., Chen, C., Qiu, H., Yang, R.G., 2011. Down-regulation of HIV-1 infection by inhibition of the MAPK signaling pathway. Virol. Sin. https://doi.org/10.1007/s12250-011-3184-y.

Herbein, G., Gras, G., Khan, K., Abbas, W., 2010. Macrophage signaling in HIV-1 infection. Retrovirology 7, 34. https://doi.org/10.1186/1742-4690-7-34.

Idriss, H.T., Naismith, J.H., 2000. TNFα and the TNF receptor superfamily: structure-function relationship(s). Microsc. Res. Tech. 50, 184–195. https://doi.org/10.1002/1097-0029(20000801)50:3<184::AID-JEMT2>3.0.CO;2-H.

Kozakov, D., Hall, D.R., Xia, B., Porter, K.A., Padhorny, D., Yueh, C., Beglov, D., Vajda, S., 2017. The ClusPro web server for protein–protein docking. Nat. Protoc. 12, 255–278. https://doi.org/10.1038/nprot.2016.169.

Kruize, Z., Kootstra, N.A., 2019. The role of macrophages in HIV-1 persistence and pathogenesis. Front. Microbiol. 10, 1–17. https://doi.org/10.3389/fmicb.2019.02828.

Kumar, A., Abbas, W., Herbein, G., 2013. TNF and TNF receptor superfamily members in HIV infection: new cellular targets for therapy? Mediat. Inflamm. 2013 https://doi.org/10.1155/2013/484378.

Li, J., Yin, Q., Wu, H., 2013. Structural basis of signal transduction in the TNF receptor superfamily. Adv. Immunol. 1–17 https://doi.org/10.1016/B978-0-12-407707-2.00005-9.Structural.

Li, Z., Wu, J., Chavez, L., Hoh, R., Deeks, S.G., Pillai, S.K., Zhou, Q., 2019. Reiterative enrichment and authentication of CRISPRi targets (REACT) identifies the proteasome as a key contributor to HIV-1 latency. PLoS Pathog. 15, 1–21. https://doi.org/10.1371/journal.ppat.1007498.

Mbita, Z., Hull, R., Dlamini, Z., 2014. Human immunodeficiency virus-1 (HIV-1)-mediated apoptosis: new therapeutic targets. Viruses 6, 3181–3227. https://doi.org/10.3390/v6083181.

Möhle, K., Gußmann, M., Hofmann, H.J., 1997. Structural and energetic relations between β turns. J. Comput. Chem. 18, 1415–1430. https://doi.org/10.1002/(SICI)1096-987X(199708)18:11<1415::AID-JCC8>3.0.CO;2-O.

Mukai, Y., Nakamura, T., Yoshikawa, M., Yoshioka, Y., 2013. Solution of the Structure of the TNF-TNFR2 Complex 3. https://doi.org/10.1126/scisignal.2000954.

Ouellet, M., Mercier, S., Pelletier, I., Bounou, S., Roy, J., Hirabayashi, J., Sato, S., Tremblay, M.J., 2005. Galectin-1 acts as a soluble host factor that promotes HIV-1 infectivity through stabilization of virus attachment to host cells. J. Immunol. 174, 4120–4126. https://doi.org/10.4049/jimmunol.174.7.4120.

Perl, A., Banki, K., 2000. Genetic and metabolic control of the mitochondrial transmembrane potential and reactive oxygen intermediate production in HIV disease. Antioxid. Redox Signal. 2, 551–573. https://doi.org/10.1089/15230860050192323.

Pettersen, E.F., Goddard, T.D., Huang, C.C., Couch, G.S., Greenblatt, D.M., Meng, E.C., Ferrin, T.E., 2004. UCSF chimera - a visualization system for exploratory research and analysis. J. Comput. Chem. 25, 1605–1612. https://doi.org/10.1002/jcc.20084.

Pitrak, D.L., Novak, R.M., Estes, R., Tschampa, J., Abaya, C.D., Martinson, J., Bradley, K., Tenorio, A.R., Landay, A.L., 2014. Apoptosis pathways in HIV-1-infected patients before and after highly active antiretroviral therapy: relevance to immune recovery. AIDS Res. Hum. Retrovir. 30, 1–9.

Ruffin, N., Gea-Mallorquí, E., Brouiller, F., Jouve, M., Silvin, A., See, P., Dutertre, C.A., Ginhoux, F., Benaroch, P., 2019. Constitutive Siglec-1 expression confers susceptibility to HIV-1 infection of human dendritic cell precursors. Proc. Natl. Acad. Sci. U. S. A. 116, 21685–21693. https://doi.org/10.1073/pnas.1911007116.

Sedaghat, A.R., German, J., Teslovich, T.M., Cofrancesco, J., Jie, C.C., Talbot, C.C., Siliciano, R.F., 2008. Chronic CD4+ T-cell activation and depletion in human immunodeficiency virus type 1 infection: type I interferon-mediated disruption of T-cell dynamics. J. Virol. 82, 1870–1883. https://doi.org/10.1128/jvi.02228-07.

Steeland, S., Libert, C., Vandenbroucke, R.E., 2018. A new venue of TNF targeting. Int. J. Mol. Sci. 19, 1–55. https://doi.org/10.3390/ijms19051442.

Su, Z., Wu, Y., 2020. A computational model for understanding the oligomerization mechanisms of TNF receptor superfamily. Comput. Struct. Biotechnol. J. https://doi.org/10.1016/j.csbj.2019.12.016.

Tian, J., López, C.A., Derdeyn, C.A., Jones, M.S., Pinter, A., Korber, B., Gnanakaran, S., 2016. Effect of glycosylation on an Immunodominant region in the V1V2 variable domain of the HIV-1 envelope gp120 protein. PLoS Comput. Biol. 12, 1–33. https://doi.org/10.1371/journal.pcbi.1005094.

Vivès, R.R., Imberty, A., Sattentau, Q.J., Lortat-Jacob, H., 2005. Heparan sulfate targets the HIV-1 envelope glycoprotein gp120 coreceptor binding site. J. Biol. Chem. 280, 21353–21357. https://doi.org/10.1074/jbc.M500911200.

Wajant, H., Siegmund, D., 2019. TNFR1 and TNFR2 in the control of the life and death balance of macrophages. Front. Cell Dev. Biol. 7, 1–14. https://doi.org/10.3389/fcell.2019.00091.

Wallace, A.C., Laskowski, R.A., Thornton, J.M., 1995. LIGPLOT: A Program to Generate Schematic Diagrams of Protein-Ligand Interactions Clean up Structure, 8, pp. 127–134.

Yang, S., Wang, J., Brand, D.D., Zheng, S.G., 2018. Role of TNF-TNF receptor 2 signal in regulatory T cells and its therapeutic implications. Front. Immunol. 9 https://doi.org/10.3389/fimmu.2018.00784.

Yoon, V., Fridkis-Hareli, M., Munisamy, S., Lee, J., Anastasiades, D., Stevceva, L., 2010. The GP120 molecule of HIV-1 and its interaction with T cells. Curr. Med. Chem. 17, 741–749. https://doi.org/10.2174/092986710790514499.