Article

Two Achilles' Heels of the Ebolavirus Glycoprotein?

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Abstract: Ebolavirus has a membrane envelope decorated by trimers of a glycoprotein (GP), which is responsible for host cell attachment and membrane fusion. Therefore, GP is a primary target for antiviral drugs development. Here, this article reports the first, to my knowledge, set of structural analysis of all Ebolavirus GP structures as of March 10, 2020, and also a brief update of the structurally identified electrostatic features of the Ebolavirus GP structures in both apo (unliganded) state and also in bound states with a series of small compounds, including a variety of approved drugs. With this comprehensive set of structural analysis, this article puts forward a hypothesis of two Achilles' heels of Ebolavirus GP structure, where the formation of two interfacial salt bridges, instead of destabilizing the prefusion conformation of Ebolavirus GP, constitutes a positive contribution towards the structural rigidification of the prefusion conformation of the Ebolavirus GP structure, thereby acting against GP-mediated Ebolavirus cell entry and/or preventing fusion between the viral and endosome membranes.

Keywords: Ebolavirus glycoprotein; Electrostatic interaction; Salt bridging network; Two Achilles' heels

1. Introduction

Ebolavirus is a rare but deadly virus that causes fever, body aches, and diarrhoea, and sometimes bleeding inside and outside the body [1–13]. Structurally, Ebolavirus has a membrane envelope decorated by trimers of a glycoprotein, i.e., GP, which is cleaved by furin to form GP1 and GP2 subunits [14–49]. Functionally, GP is responsible for host cell attachment, endosomal entry and membrane fusion, making it a critical target for the development of antiviral drugs [17,50,50–57].

2. Motivation

Experimental studies around the Ebolavirus disease, both fundamental and clinical, have been reported extensively in recent years [58–114]. For instance, a set of Ebolavirus GP experimental structures were reported [14–16,115–117], including both apo (unliganded) structure of Ebolavirus GP, and also high-resolution complex structures of GP with a series of directly interacting compounds (including a variety of approved drugs) and also its neutralizing antibodies (Tables 1 and 2).

While the recent structural studies [14–16,115–117] painted an overall experimental picture of the Ebolavirus GP molecule, allowing conformational changes induced by antibody and receptor binding to be deciphered, in-depth structural and functional details, including its mechanism of inhibition, i.e., action mode of mediating virus cell entry [118–125] and possible conformational dynamics associated with it, are still to be investigated further, both experimentally and computationally [126,127]. As previously reported, the protein–drug interactions with both GP1 and GP2 are predominately hydrophobic [14–16,115–117], thus, from a structural point of view, this article aims to extract all electrostatic features embedded in all experimentally determined Ebolavirus GP structures currently available as of March 10, 2020.

3. Materials and Methods

As of March 10, 2020, the Protein Data Bank (PDB) [128] hosts 36 Ebolavirus glycoprotein structures, as listed in Table 1 below,

No.	PDB ID	Structure Title
1	1EBO	Crystal structure of the Ebolavirus membrane-fusion subunit, gp2, from the envelope glycoprotein ectodomain
2	2EBO	Core structure of gp2 from Ebolavirus
3	2QHR	Crystal structure of the 13f6-1-2 fab fragment bound to its Ebolavirus glycoprotein peptide epitope.
4	2RLJ	NMR structure of Ebola fusion peptide in SDS micelles at pH 7
5	2Y6S	Structure of an Ebolavirus-protective antibody in complex with its mucin-domain linear epitope
6	3CSY	Crystal structure of the trimeric prefusion Ebolavirus glycoprotein in complex with a neutralizing antibody from a human survivor
7	3VE0	Crystal structure of sudan Ebolavirus glycoprotein (strain boniface) bound to 16f6
8	5F1B	Structural basis of Ebolavirus entry: viral glycoprotein bound to its endosomal receptor Niemann-Pick C1
9	5FHC	Crystal Structure of Protective Human Antibodies 100 and 114 in Complex with Ebola Virus Fusion Glycoprotein (GP)
10	5HJ3	Crystal structure of host-primed Ebolavirus GP, GPcl
11	5JNX	The 6.6 Å Cryo-EM structure of the full-length human NPC1 in complex with the cleaved glycoprotein of Ebolavirus
12	5JQ3	Crystal structure of Ebola glycoprotein
13	5JQ7	Crystal structure of Ebola glycoprotein in complex with toremifene
14	5JQB	Crystal structure of Ebola glycoprotein in complex with ibuprofen
15	5KEL	EBOV GP in complex with variable Fab domains of IgGs c2G4 and c13C6
16	5KEM	EBOV sGP in complex with variable Fab domains of IgGs c13C6 and BDBV91
17	5KEN	EBOV GP in complex with variable Fab domains of IgGs c4G7 and c13C6
18	5T42	Structure of the Ebolavirus envelope protein MPER/TM domain and its interaction with the fusion loop explains their fusion activity
19	6DZL	Ebolavirus Makona variant GP (mucin-deleted) in complex with pan-ebolavirus human antibody ADI-15878 Fab
20	6EA7	Structure of EBOV GPcl in complex with the pan-ebolavirus mAb ADI-15878
21	6F5U	Crystal structure of Ebolavirus glycoprotein in complex with bepridil
22	6F6I	Crystal structure of Ebolavirus glycoprotein in complex with paroxetine
23	6F6N	Crystal structure of Ebolavirus glycoprotein in complex with sertraline
24	6F6S	Crystal structure of Ebolavirus glycoprotein in complex with benztropine
25	6G95	Crystal structure of Ebolavirus glycoprotein in complex with thioridazine
26	6G9B	Crystal structure of Ebolavirus glycoprotein in complex with imipramine
27	6G9I	Crystal structure of Ebolavirus glycoprotein in complex with clomipramine
28	6HRO	Crystal structure of Ebolavirus glycoprotein in complex with inhibitor 118a
29	6HS4	Crystal structure of Ebolavirus glycoprotein in complex with inhibitor 118
30	6MAM	Cleaved Ebola gp in complex with a broadly neutralizing human antibody, adi-15946
31	6NAE	Crystal Structure of Ebola zaire GP protein with bound ARN0074898
32	6QD7	EM structure of a EBOV-GP bound to 3T0331 neutralizing antibody
33	6QD8	EM structure of a EBOV-GP bound to 4M0368 neutralizing antibody
34	6S8D	Structure of ZEBOV GP in complex with 1T0227 antibody
35	6S8I	Structure of ZEBOV GP in complex with 3T0265 antibody
36	6S8J	Structure of ZEBOV GP in complex with 5T0180 antibody

Table 1. Experimentally determined Ebolavirus GP structures inside Protein Data Bank (PDB [128]) as of March 10, 2020 with a **Text Search** for: ebola glycoprotein and **Molecule:** Envelope glycoprotein.

Among the 36 in Table 1, 12 were experimentally determined structures of Ebolavirus glycoprotein in complex with a set of compounds (Table 2), including a variety of approved drugs [14–16,115–117].

No.	PDB ID	Structure Title
12	5JQ3	Crystal structure of Ebola glycoprotein
13	5JQ7	Crystal structure of Ebola glycoprotein in complex with toremifene
14	5JQB	Crystal structure of Ebola glycoprotein in complex with ibuprofen
21	6F5U	Crystal structure of Ebolavirus glycoprotein in complex with bepridil
22	6F6I	Crystal structure of Ebolavirus glycoprotein in complex with paroxetine
23	6F6N	Crystal structure of Ebolavirus glycoprotein in complex with sertraline
24	6F6S	Crystal structure of Ebolavirus glycoprotein in complex with benztropine
25	6G95	Crystal structure of Ebolavirus glycoprotein in complex with thioridazine
26	6G9B	Crystal structure of Ebolavirus glycoprotein in complex with imipramine
27	6G9I	Crystal structure of Ebolavirus glycoprotein in complex with clomipramine
28	6HRO	Crystal structure of Ebolavirus glycoprotein in complex with inhibitor 118a
29	6HS4	Crystal structure of Ebolavirus glycoprotein in complex with inhibitor 118

Table 2. Experimentally determined structures of Ebolavirus GP in complex with a series of small molecules as of March 10, 2020. In this table, the numbers in the first column are taken directly from Table 1.

After all 36 structures (Table 1) were accessed and downloaded directly from the PDB website [128], a comprehensive set of electrostatic interaction (including salt bridging and hydrogen bonding) analysis was subsequently carried out as described in [129] previously.

4. Results

4.1. Electrostatic features embedded inside Ebolavirus glycoprotein structures: a brief update

With the electrostatic analysis as described previously in [129], this article puts forward a comprehensive set of electrostatic interaction features for the 36 Ebolavirus glycoprotein structures as of March 10, 2020, all included as a large set of separate tables in the supplementary file **supplementary.pdf**, including specifically:

1. all salt bridges formed within the 36 Ebolavirus glycoprotein structures as of March 10, 2020.
2. all interfacial salt bridges formed within the 36 Ebolavirus glycoprotein structures as of March 10, 2020.
3. all salt bridges formed within the 36 Ebolavirus glycoprotein structures as of March 10, 2020 PDB ID-specifically.
4. all interfacial salt bridges formed within the 36 Ebolavirus glycoprotein structures as of March 10, 2020 PDB ID-specifically.
5. all main and side chains hydrogen bonds formed within the 36 Ebolavirus glycoprotein structures as of March 10, 2020.
6. all side chain hydrogen bonds formed within the 36 Ebolavirus glycoprotein structures as of March 10, 2020.
7. all main and side chains hydrogen bonds formed within the 36 Ebolavirus glycoprotein structures as of March 10, 2020 PDB ID-specifically.
8. all side chain hydrogen bonds formed within the 36 Ebolavirus glycoprotein structures as of March 10, 2020 PDB ID-specifically.

4.2. An electrostatic investigation into the complex structures of Ebolavirus GP bound to small molecules

This article aims to delve into the experimentally determined complex structures of Ebolavirus GP bound to small molecules [14–16,115–117]. Thus, from Table 1, all complex structures of Ebolavirus GP bound to small molecules were singled out and listed in Tables 2 and 3, respectively, where the second and the third columns of Table 3 are taken directly from Table 2, as listed below.

Salt bridging analysis	PDB ID	Structure Title in Abstract
Initial template structure for interfacial differential salt bridging analysis	5JQ3	GP
B_LYS_510-A_GLU_292	5JQ7	GP + toremifene
B_LYS_510-A_GLU_292,B_LYS_510-A_GLU_292,B_LYS_588-A_ASP_47,B_LYS_588-A_ASP_47	5JQB	GP + ibuprofen
B_LYS_510-A_GLU_292	6F5U	GP + bepridil
B_LYS_510-A_GLU_292	6F6I	GP + paroxetine
B_LYS_510-A_GLU_292,B_LYS_588-A_ASP_47,B_LYS_588-A_ASP_47	6F6N	GP + sertraline
B_LYS_510-A_GLU_292,B_LYS_510-A_GLU_292,B_LYS_588-A_ASP_47,B_LYS_588-A_ASP_47	6F6S	GP + benzotropine
	6G95	GP + thioridazine
B_LYS_510-A_GLU_292,B_LYS_588-A_ASP_47,B_LYS_588-A_ASP_47	6G9B	GP + imipramine
	6G9I	GP + clomipramine
B_LYS_510-A_GLU_292,B_LYS_588-A_ASP_47,B_LYS_588-A_ASP_47	6HRO	GP + inhibitor 118a
B_LYS_588-A_ASP_47,B_LYS_588-A_ASP_47	6HS4	GP + inhibitor 118

Table 3. A differential analysis of the interfacial salt bridging analysis of the experimentally determined structures of Ebolavirus GP in complex with small molecules as of March 10, 2020. In this table, the second and the third columns are taken directly from Table 1, while the first column represents the differential salt bridging analysis of the 11 structures against the apo unliganded crystal structure of GP (PDB ID: 5JQ3, the initial template structure for the differential salt bridging analysis). Moreover, the B_LYS_588-A_ASP_47 represents the interfacial salt bridge formed due to the presence of the small molecules compared with the apo-state Ebolavirus GP structure, while the B_LYS_510-A_GLU_292 represents the interfacial salt bridge formed due to the presence of the small molecules compared with the apo-state Ebolavirus GP structure, too. Furthermore in this table, the residue naming scheme is Chain ID_residue name_residue number, the residue pair naming scheme is Chain ID_residue name_residue number-Chain ID_residue name_residue number.

A differential salt bridging analysis between 5JQ3 and 5JQ7 (Table 3)
Common salt bridges between 5JQ3 and 5JQ7
A_HIS_39-A_ASP_55
A_HIS_39-A_ASP_55
A_ARG_85-A_GLU_178
A_ARG_85-A_GLU_178
A_LYS_114-A_GLU_120
A_LYS_114-A_GLU_120
A_ARG_130-A_ASP_163
A_HIS_154-A_GLU_178
A_ARG_164-A_ASP_163
A_ARG_164-A_ASP_163
A_ARG_266-A_ASP_237
B_HIS_516-B_GLU_545
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
Structurally identified 5JQ3-only salt bridges
No 5JQ3-only salt bridge was structurally identified here
Structurally identified 5JQ7-only salt bridges
A_ARG_247-A_GLU_245

A_ARG_247-A_GLU_245
B_LYS_510-A_GLU_292
B_HIS_613-B_ASP_614
A differential salt bridging analysis between 5JQ3 and 5JQB (Table 3)
Common salt bridges between 5JQ3 and 5JQB
A_ARG_85-A_GLU_178
A_ARG_85-A_GLU_178
A_LYS_114-A_GLU_120
A_LYS_114-A_GLU_120
A_ARG_130-A_ASP_163
A_HIS_154-A_GLU_178
A_ARG_164-A_ASP_163
A_ARG_164-A_ASP_163
A_ARG_266-A_ASP_237
B_HIS_516-B_GLU_545
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
Structurally identified 5JQ3-only salt bridges
A_HIS_39-A_ASP_55
A_HIS_39-A_ASP_55
Structurally identified 5JQB-only salt bridges
A_ARG_247-A_GLU_245
B_LYS_510-A_GLU_292
B_LYS_510-A_GLU_292
B_LYS_588-A_ASP_47
B_LYS_588-A_ASP_47
B_LYS_617-B_ASP_614
A differential salt bridging analysis between 5JQ3 and 6F5U (Table 3)
Common salt bridges between 5JQ3 and 6F5U
A_HIS_39-A_ASP_55
A_HIS_39-A_ASP_55
A_ARG_85-A_GLU_178
A_ARG_85-A_GLU_178
A_LYS_114-A_GLU_120
A_LYS_114-A_GLU_120
A_ARG_130-A_ASP_163
A_HIS_154-A_GLU_178
A_ARG_164-A_ASP_163
A_ARG_164-A_ASP_163
A_ARG_266-A_ASP_237
B_HIS_516-B_GLU_545
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
Structurally identified 5JQ3-only salt bridges

No 5JQ3-only salt bridge was structurally identified here
Structurally identified 6F5U-only salt bridges
A_ARG_247-A_GLU_245
B_LYS_510-A_GLU_292
A differential salt bridging analysis between 5JQ3 and 6F6I (Table 3)
Common salt bridges between 5JQ3 and 6F6I
A_ARG_85-A_GLU_178
A_ARG_85-A_GLU_178
A_LYS_114-A_GLU_120
A_LYS_114-A_GLU_120
A_ARG_130-A_ASP_163
A_HIS_154-A_GLU_178
A_ARG_164-A_ASP_163
A_ARG_164-A_ASP_163
A_ARG_266-A_ASP_237
B_HIS_516-B_GLU_545
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
Structurally identified 5JQ3-only salt bridges
A_HIS_39-A_ASP_55
A_HIS_39-A_ASP_55
Structurally identified 6F6I-only salt bridges
A_LYS_140-A_GLU_112
A_ARG_247-A_GLU_245
B_LYS_510-A_GLU_292
B_HIS_628-B_ASP_629
B_HIS_628-B_ASP_629
A differential salt bridging analysis between 5JQ3 and 6F6N (Table 3)
Common salt bridges between 5JQ3 and 6F6N
A_ARG_85-A_GLU_178
A_ARG_85-A_GLU_178
A_LYS_114-A_GLU_120
A_LYS_114-A_GLU_120
A_ARG_130-A_ASP_163
A_HIS_154-A_GLU_178
A_ARG_164-A_ASP_163
A_ARG_164-A_ASP_163
A_ARG_266-A_ASP_237
B_HIS_516-B_GLU_545
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
Structurally identified 5JQ3-only salt bridges
A_HIS_39-A_ASP_55
A_HIS_39-A_ASP_55

Structurally identified 6F6N-only salt bridges
A_LYS_50-A_ASP_49
A_LYS_50-A_ASP_49
A_ARG_247-A_GLU_245
A_LYS_276-A_GLU_245
B_LYS_510-A_GLU_292
B_LYS_588-A_ASP_47
B_LYS_588-A_ASP_47
A differential salt bridging analysis between 5JQ3 and 6F6S (Table 3)
Common salt bridges between 5JQ3 and 6F6S
A_ARG_85-A_GLU_178
A_ARG_85-A_GLU_178
A_LYS_114-A_GLU_120
A_LYS_114-A_GLU_120
A_ARG_130-A_ASP_163
A_HIS_154-A_GLU_178
A_ARG_164-A_ASP_163
A_ARG_164-A_ASP_163
B_HIS_516-B_GLU_545
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
Structurally identified 5JQ3-only salt bridges
A_HIS_39-A_ASP_55
A_HIS_39-A_ASP_55
A_ARG_266-A_ASP_237
Structurally identified 6F6S-only salt bridges
B_LYS_510-A_GLU_292
B_LYS_510-A_GLU_292
B_LYS_588-A_ASP_47
B_LYS_588-A_ASP_47
B_LYS_617-B_ASP_614
A differential salt bridging analysis between 5JQ3 and 6G95 (Table 3)
Common salt bridges between 5JQ3 and 6G95
A_HIS_39-A_ASP_55
A_HIS_39-A_ASP_55
A_ARG_85-A_GLU_178
A_ARG_85-A_GLU_178
A_LYS_114-A_GLU_120
A_LYS_114-A_GLU_120
A_ARG_130-A_ASP_163
A_HIS_154-A_GLU_178
A_ARG_164-A_ASP_163
A_ARG_164-A_ASP_163
A_ARG_266-A_ASP_237
B_HIS_516-B_GLU_545
B_ARG_559-A_GLU_103

B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
Structurally identified 5JQ3-only salt bridges
No 5JQ3-only salt bridge was structurally identified here
Structurally identified 6G95-only salt bridges
A_LYS_140-A_GLU_112
A differential salt bridging analysis between 5JQ3 and 6G9B (Table 3)
Common salt bridges between 5JQ3 and 6G9B
A_ARG_85-A_GLU_178
A_ARG_85-A_GLU_178
A_LYS_114-A_GLU_120
A_LYS_114-A_GLU_120
A_ARG_130-A_ASP_163
A_HIS_154-A_GLU_178
A_ARG_164-A_ASP_163
A_ARG_164-A_ASP_163
A_ARG_266-A_ASP_237
B_HIS_516-B_GLU_545
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
Structurally identified 5JQ3-only salt bridges
A_HIS_39-A_ASP_55
A_HIS_39-A_ASP_55
Structurally identified 6G9B-only salt bridges
A_LYS_140-A_GLU_112
A_ARG_172-A_GLU_120
A_ARG_247-A_GLU_245
B_LYS_510-A_GLU_292
B_LYS_588-A_ASP_47
B_LYS_588-A_ASP_47
B_LYS_617-B_ASP_614
B_HIS_628-B_ASP_629
B_HIS_628-B_ASP_629
A differential salt bridging analysis between 5JQ3 and 6G9I (Table 3)
Common salt bridges between 5JQ3 and 6G9I
A_HIS_39-A_ASP_55
A_HIS_39-A_ASP_55
A_ARG_85-A_GLU_178
A_ARG_85-A_GLU_178
A_LYS_114-A_GLU_120
A_LYS_114-A_GLU_120
A_ARG_130-A_ASP_163
A_HIS_154-A_GLU_178
A_ARG_164-A_ASP_163
A_ARG_164-A_ASP_163

A_ARG_266-A_ASP_237
B_HIS_516-B_GLU_545
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
Structurally identified 5JQ3-only salt bridges
No 5JQ3-only salt bridge was structurally identified here
Structurally identified 6G9I-only salt bridges
B_LYS_622-B_ASP_621
B_LYS_622-B_ASP_621
A differential salt bridging analysis between 5JQ3 and 6HRO (Table 3)
Common salt bridges between 5JQ3 and 6HRO
A_ARG_85-A_GLU_178
A_ARG_85-A_GLU_178
A_LYS_114-A_GLU_120
A_LYS_114-A_GLU_120
A_ARG_130-A_ASP_163
A_HIS_154-A_GLU_178
A_ARG_164-A_ASP_163
A_ARG_164-A_ASP_163
A_ARG_266-A_ASP_237
B_HIS_516-B_GLU_545
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
Structurally identified 5JQ3-only salt bridges
A_HIS_39-A_ASP_55
A_HIS_39-A_ASP_55
Structurally identified 6HRO-only salt bridges
B_LYS_510-A_GLU_292
B_LYS_588-A_ASP_47
B_LYS_588-A_ASP_47
A differential salt bridging analysis between 5JQ3 and 6HS4 (Table 3)
Common salt bridges between 5JQ3 and 6HS4
A_HIS_39-A_ASP_55
A_HIS_39-A_ASP_55
A_ARG_85-A_GLU_178
A_ARG_85-A_GLU_178
A_LYS_114-A_GLU_120
A_LYS_114-A_GLU_120
A_ARG_130-A_ASP_163
A_HIS_154-A_GLU_178
A_ARG_164-A_ASP_163
A_ARG_164-A_ASP_163
A_ARG_266-A_ASP_237
B_HIS_516-B_GLU_545

B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
B_ARG_559-A_GLU_103
Structurally identified 5JQ3-only salt bridges
No 5JQ3-only salt bridge was structurally identified here
Structurally identified 6HS4-only salt bridges
B_LYS_588-A_ASP_47
B_LYS_588-A_ASP_47

Table 4. PDBID-specific comparison of structurally identified salt bridging networks of Ebolavirus GP in complex with small molecules (Table 3). In this table, the texts in black represent the structurally identified salt bridges that exist in both apo- and bound-state of the Ebolavirus GP, the texts in green represent the structurally identified salt bridges only in apo-state Ebolavirus GP, while the texts in red represent the structurally identified salt bridges only in the 11 bound-state Ebolavirus GPs, respectively. In addition, in this table, the residue naming scheme is **Chain ID_residue name_residue number**, the residue pair naming scheme is **Chain ID_residue name_residue number-Chain ID_residue name_residue number**.

4.3. A hypothesis of two Achilles’ heels of the Ebolavirus glycoprotein

This article aims to delve into the experimentally determined complex structures of Ebolavirus GP bound to small molecules [14–16,115–117]. Instead of focusing on the common structurally identified salt bridges that exist in both apo- and bound-state of the Ebolavirus GP (Table 4 and Figure 1), this article focused on the structurally identified salt bridges, which are absent in the apo unliganded structure of Ebolavirus GP, but which are present in the 11 bound-state of structure of Ebolavirus GPs (Tables 2 and 3).

Figure 1. An overall structure of the Ebolavirus glycoprotein in complex with Ibuprofen. In this figure, the Ebolavirus GP is shown as green (chain A: ENVELOPE GLYCOPROTEIN 1) and cyan (chain B: ENVELOPE GLYCOPROTEIN 2) cartoon, while ibuprofen Tables 3 and 4 is shown as dark blue sticks. This figure is prepared using PyMol [130] with 5JQB.pdb (Table 1) as an input.

As reported previously [14–16,115–117], binding of the small molecules destabilizes the Ebolavirus GP, such as the cases for the anticancer drug toremifene and the painkiller ibuprofen, which bind in the same large cavity on the glycoprotein [14–16,115–117]. Furthermore, crystal structures show that the position of binding and the mode of interaction within the pocket vary significantly between these compounds, which is in agreement with the protein-inhibitor interactions as well as with the antiviral activities determined by virus cell entry assays [14–16,115–117]. While it is likely that this difference stems from the various chemical structures of these small compounds, it is also likely that there are common features in the way these small compounds cause structural perturbations/disturbances to Ebolavirus GP, as evidenced by the structural electrostatic analysis listed in Tables 3 and 4, and illustrated below in Figures 2, 3, 4, 5, 6 and 7, respectively.

Figure 2. A hypothesis of two Achilles' heels of the Ebolavirus glycoprotein. In this figure, the first hypothesized Achilles' heel is shown as the two structurally identified interfacial salt bridges between B_LYS_510 and A_GLU_292 (Table 3), which helps restrain the inter-chain conformational flexibility of Ebolavirus GP, and also contributes to local inter-chain structural rigidification [131] of Ebolavirus GP, as shown approximately in the region inside the box in orange. This figure is prepared using PyMol [130] with 5JQB.pdb (Table 1) as an input with other details the same as that described in Figure 1.

Figure 3. A hypothesis of two Achilles' heels of the Ebolavirus glycoprotein. In this figure, the first hypothesized Achilles' heel is shown as the two structurally identified interfacial salt bridges (two yellow dotted lines) between B_LYS_510 and A_GLU_292 (Table 3), which helps restrain the inter-chain conformational flexibility of Ebolavirus GP, and also contributes to local inter-chain structural rigidification [131] of Ebolavirus GP, as shown approximately in the region inside the box in orange. This figure is prepared using PyMol [130] with 5JQB.pdb (Table 1) as an input with other details the same as that described in Figure 1.

Figure 4. A hypothesis of two Achilles' heels of the Ebolavirus glycoprotein. In this figure, the first hypothesized Achilles' heel is shown as the two structurally identified interfacial salt bridges (two yellow dotted lines with two labels 3.9 and 2.7 Å as their respective lengths) between B_LYS_510 and A_GLU_292 (Table 3), which helps restrain the inter-chain conformational flexibility of Ebolavirus GP, and also contributes to local inter-chain structural rigidification [131] of Ebolavirus GP. This figure is prepared using PyMol [130] with 5JQB.pdb (Table 1) as an input with other details the same as that described in Figure 1.

Figure 5. A hypothesis of two Achilles' heels of the Ebolavirus glycoprotein. In this figure, the second hypothesized Achilles' heel is shown as the two structurally identified interfacial salt bridges between B_LYS_588 and A_ASP_47 (Table 3), which helps restrain the inter-chain conformational flexibility of Ebolavirus GP, and also contributes to local inter-chain structural rigidification [131] of Ebolavirus GP, as shown approximately in the region inside the box in red. This figure is prepared using PyMol [130] with 5JQB.pdb (Table 1) as an input with other details the same as that described in Figure 1.

Figure 6. A hypothesis of two Achilles' heels of the Ebolavirus glycoprotein. In this figure, the second hypothesized Achilles' heel is shown as the two structurally identified interfacial salt bridges (two yellow dotted lines) between B_LYS_588 and A_ASP_47 (Table 3), which helps restrain the inter-chain conformational flexibility of Ebolavirus GP, and also contributes to local inter-chain structural rigidification [131] of Ebolavirus GP. This figure is prepared using PyMol [130] with 5JQB.pdb (Table 1) as an input with other details the same as that described in Figure 1.

Figure 7. A hypothesis of two Achilles' heels of the Ebolavirus glycoprotein. In this figure, the second hypothesized Achilles' heel is shown as the two structurally identified interfacial salt bridges (two yellow dotted lines with two labels 3.1 and 3.6 Å as their respective lengths) between B_LYS_588 and A_ASP_47 (Table 3), which helps restrain the inter-chain conformational flexibility of Ebolavirus GP, and also contributes to local inter-chain structural rigidification [131] of Ebolavirus GP. This figure is prepared using PyMol [130] with 5JQB.pdb (Table 1) as an input with other details the same as that described in Figure 1.

Specifically, the two hypothesized Achilles' heels consist of two inter-chain salt bridges, i.e., **B_LYS_510-A_GLU_292** (Figures 2, 3 and 4) and **B_LYS_588-A_ASP_47** (Figures 5, 6 and 7), respectively. According to the structural electrostatic analysis [129], the apo unliganded Ebolavirus GP does not form any **B_LYS_510-A_GLU_292** salt bridge, with the distances between charged atoms (two side chain carbonyl oxygens and one side chain nitrogen) being 4.7 and 6.6 Å, respectively. Nor does the apo unliganded Ebolavirus GP form any **B_LYS_588-A_ASP_47** salt bridge, with the distances between charged atoms (two side chain carbonyl oxygens and one side chain nitrogen) being 13.4 and 11.6 Å, respectively.

To define this two Achilles' heel hypothesis, I take PDB ID (5JQB) as an example, which represents an experimentally determined complex structure of Ebolavirus GP and ibuprofen Table 1. In this hypothesis, the **B_LYS_510-A_GLU_292** (Figures 2, 3 and 4) salt bridge allows chain B (via **B_LYS_510**) to restrain the inter-chain conformational flexibility of chain A (via **A_GLU_292**), contributing to local inter-chain structural rigidification [131], while the **B_LYS_588-A_ASP_47** (Figures 5, 6 and 7) salt bridge allows chain A (via **A_ASP_47**) to restrain the inter-chain conformational flexibility of chain B (via **B_LYS_588**), contributing to local inter-chain structural rigidification [131], as shown in Figures 5, 6 and 7. This two Achilles' heel hypothesis highlights the functional importance of the conformational flexibility of the approximate structural region in the orange box (Figures 2 and 3) and the approximate structural region in the red box (Figure 5) in GP-mediated Ebolavirus cell entry and/or membrane-fusion. Quite similarly, according to a previously reported computational study [131], $\alpha_2\delta$ -1-bound gabapentin establishes an electrostatic axis consisting of Q535 (Gln535)-R241 (Arg241)-GBP (gabapentin)-D452 (Asp452), which constitutes an energetically favourable contribution towards the structural stability of the $\alpha_2\delta$ -1-GBP complex and helps restrain the conformational flexibility and local structural rigidification of $\alpha_2\delta$ -1, and that GBP-induced local conformational

inflexibility and structural rigidification of $\alpha_2\delta$ -1 is one key step in the pharmacological disruption of VGCC trafficking by GBP [132–142].

5. Conclusion and Discussion

For the first time, this article reports a comprehensive set of electrostatic features embedded inside currently (as of March 10, 2020) available Ebolavirus GP structures inside PDB [128] in both PDF format (supplementary file **supplementary.pdf**) and also $\text{\LaTeX}$ format, i.e., a series of machine-readable -importable and -analyzable .tex files zipped in the supplementary file **scan.zip**. In supplementary file **scan.zip**, a simple python-based analysis tool and a $\text{\LaTeX}$ -based editing tool [143] were included to extract and summarize the electrostatic features from experimentally determined structures, where a set of PDB files (representing experimentally determined protein structures) are to be plugged into a set of python scripts included in **cmd.py**. Afterwards, **cmd.py** is to be executed with a simple command (**python cmd.py**) on a Linux machine terminal to produce the final supplementary file **supplementary.pdf**, summarizing the structurally observed electrostatic features of the 36 Ebolavirus GP-related experimental structures as of March 10, 2020.

Moreover, this article puts forward a set of small molecule-induced perturbation of interfacial electrostatic interaction network within experimentally determined ebola GP structures, and hypothesizes that these small compounds inhibit viral cell entry and/or membrane-fusion by binding to the glycoprotein, inducing a minor conformational perturbation, leading to the establishment of two inter-chain salt bridges, i.e., **B_LYS_510-A_GLU_292** (Figures 2, 3 and 4) and **B_LYS_588-A_ASP_47** (Figures 5, 6 and 7), restraining the conformational flexibility of the approximate structural region in the orange box (Figures 2 and 3) and the approximate structural region in the red box (Figure 5) against GP-mediated Ebolavirus cell entry and/or membrane-fusion [14–16,115–118]. Along with previously reported details of the protein-inhibitor interactions of these complexes, this hypothesis may facilitate the design of more potent inhibitors of Ebolavirus cell entry [119–125,125,144–149] and the discovery of novel antiviral compounds [54,150–156] to prepare us for future outbreaks.

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