A study on heparin in complex with L1 protein of ten high risk Human Papillomavirus: new structural insights based on *in silico* analysis

Jorge Félix Beltrán Lissabet

Department of Biochemistry, National Center for Scientific Research, Ave 25 and 158, P.O 6412, Cubanacán, Havana City, Cuba.
jorge.beltran@cnic.edu.cu

ABSTRACT

Human papillomavirus (HPV) is one of the most common causes of sexually transmitted diseases in both men and women around the world. It has been suggested that the heparan sulfate constitute the main receptor recognized by HPV, however its role during the interactions with other HPV is not very clear. BC, DE, EF, FG, and HI are the five loops displayed on the surface of the pentamer which can interact with heparin as an analogue for heparan sulfate. In this study, the L1 late protein of ten high risks HPV (HR HPV L1) corresponding to the types 31/33/35/39/45/51/52/56/58/59 were analyzed using *in silico* methods by looking for insights related to HR HPV L1-loops and heparin interactions. The five loop regions (BC, DE, EF, FG and HI) of the ten HR HPV L1 interact with heparin, where the interaction established between the BC-loop and heparin was found to be present in all the HR HPV L1 analyzed in this study as well as those reported in the scientist literature. Moreover it was found that lysine residues are involves in most of interactions and that the charge-charge and polar interactions are stabilizing the HR HPV L1-heparin interaction. The results obtained in this work with all the *in silico* methods; suggest that the heparin-binding site in the loops for all the HR HPV plays an important role during HR HPV infections, where BC-loop constitute the most required structure during the HR HPV L1-heparin interactions. The charge-charge and polar interactions are the main forces stabilizing the HR HPV L1-heparin.

KEYWORDS: *in silico;* heparin; HPV; L1, heparan sulfate

INTRODUCTION

Human papillomavirus (HPV) is one of the most common causes of sexually transmitted diseases in both men and women around the world, with prevalence rates varying with the studied population and geographical localization.(1) HPVs can be divided into low-risk and high-risk types according to the propensity of the lesions to evolve into malignancies.(2) Twelve HPVs (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) are defined by the World Health Organization (WHO) as being high-risk cancer causing types, with additional types (68, 73) being recognized as 'possibly' cancer-causing.(3) The papillomavirus major capsid protein, L1, is a ~55 kD protein with the ability to spontaneously self-assemble into virus-like particles (VLPs). These VLPs present an exterior surface essentially indistinguishable from the native 60nm non-enveloped papillomavirus virion.(4, 5) BC, DE, EF, FG, and HI are the five loops displayed on the surface of the pentamer. These five loops constitute the part of the viral surface that can be recognized as conformational epitopes of HPV.(6) Host cell entry of HPV is initiated by binding of the virus particle to cell surface receptors. It has been suggested that virions bind initially to the basement membrane prior to transfer to the basal keratinocyte cell surface.(7, 8)

Early work investigating the cell surface receptors found that HPVs bind to a widely expressed and evolutionary conserved cell surface receptor and that the interaction depends primarily on L1.(8-12) Glycosaminoglycans, especially heparan sulfate, were suggested as initial attachment receptors for HPV VLPs.(8, 13-15) Binding to these negatively charged polysaccharides is usually electrostatic and relatively nonspecific.(16) Despite considerable efforts, (13, 14, 17-21) the interactions between HPV and the heparan sulfate oligosaccharides that initiate infection are poorly understood.(22) To date, most of the work related to the HPV L1 protein and heparan sulfate interactions using heparin as an analogue for heparan sulfate (23) covering structural aspect are very limited.

Moreover, there is a wide controversy in the scientific literature about the role of heparan sulfate as receptor for HPV. For this reason the present study is focused on the discovery of potential binding sites on the loop structures of high risk HPV L1 protein (HR HPV L1) through *in silico* strategies, in order to provide a better understanding of the establishing of heparan sulfate-HPV L1 interactions.

MATERIALS AND METHODS

The protein sequences of each high risk HPV L1 protein (HR HPV L1) used in this study were downloaded from the NCBI protein sequence database with the accession numbers [GenBank: P17388.1, P06416.1, AGU90581.1, AAY86494.1, P26536.1, ACX32362.1, P36743.1, ACL12325.1 and AGU90696.1], corresponding to HPV types 31/ 33/39/45/51/52/56/58/59, respectively. Further, the crystal structures and protein sequences of HR HPV L1 of the HPV 16/18/35 were retrieved from the Protein Data Bank (PDB) with the PDB entry ID: [PDB: 1DZL, 2R5I, 2R5J], correspondingly. Subsequently, all these protein sequences were aligned using multiple sequence comparison by log-expectation (MUSCLE) (24, 25) in order to locate the regions corresponding to loops, according to Bishop *et al* and Dasgupta *et al* (6, 22). MUSCLE utilizes a 3-stage algorithm: (1) generate a progressive alignment; (2) increase the accuracy of the progressive alignment by reconstructing a tree with the Kimura matrix and the clustering method; (3) iterative refinement of progressive alignment.

Homology modeling of the HR HPV L1

Taking into account that all crystal structures of HR HPV L1 reported to date are truncated at the N- and C-terminal (6, 22, 26), the two terminal regions of each sequences retrieved from the NCBI protein sequence database were deleted in order to generate protein models truncated with high quality, based only on templates corresponding to all HPV L1 reported in PDB. Then, the sequences with both terminal regions deleted were submitted into Phyre2 (Protein Homology/analogy Recognition Engine V 2.0) server (27), which is completely automated and determine 3D model of proteins based on multiple templates from the PDB. Also, it applies the *ab initio* folding simulation for protein modeling of regions where no templates are identified.

Refinement of protein structure models and pentamer building

All HR HPV L1 modelled with Phyre2 were refined by molecular dynamics simulation using the GalaxyRefine web server by selecting the mild and aggressive relaxation refinement mode, which perform an intensive refinement of the whole protein and its loops (28). Subsequently, all the second models refined were selected and submitted to M-ZDOCK (Symmetric Multimer Docking) server, using the symmetry option of five to generate the HPV L1 pentamers (29).

Quality assessment of protein structure models

Structural evaluation and stereochemical analyses were performed by different evaluation and validation tools before and after refinement. Backbone conformation was evaluated by analyzing the Psi/Phi Ramachandran plot obtained from PROCHECK and RAMPAGE (30, 31). Also the models were evaluated through ERRAT and PROSA web tool (32, 33).

Molecular docking

The molecular docking was performed using the program ClusPro for each monomer refined, including the native crystal structure of the HPV 35. For this process each monomer of HR HPV L1 and the heparin were chosen as receptor and ligand, respectively, by selecting the heparin mode of the program. ClusPro ranks the model solutions by cluster sizes, which were all analyzed looking for interaction among the loop regions of each monomer in complex with heparin (34). All the complexes (monomers bound to heparin) obtained in this study were visualized and analyzed using the Pymol Molecular Graphics software 1.7.0.1. Moreover, Pymol was used to observe the charge distributions of each pentamer and monomer determined with the tools mentioned above.

RESULTS AND DISCUSSIONS

Alignment

The alignment performed with the sequences retrieved from the NCBI protein sequence database and PDB, allowed the discrimination of the five loop regions (BC, DE, EF, FG and HI). Moreover, it was also observed that the N- and C-terminal sequences recovered from PDB align good with each other, which was taken into account as a benchmark in selection of amino acid regions of the sequences retrieved from NCBI for 3D modeling by removing the sequences not aligned in such extremes, since no templates based on HPV L1 are reported for these regions (Figure1). One of the main causes of removing these regions was due the C-terminal amino acids that are reported to bind DNA,(35-37) which constituted a problem in the initial dockings because of these regions can also bind heparin and thus make difficult the study of the interaction established between HR HPV L1-loops and heparin (data not shown).

Figure 1. Sequence alignment of the L1 protein of twelve high risk Human Papillomavirus showing the portion of the N-and C-terminal region deleted, and the localization of the loops BC, DE, EF, FG, and HI according to Bishop *et al* and Dasgupta *et al*.

Homology modeling of the HR HPV L1

The 3D structures of the HR HPV L1 types 31/33/39/45/51/52/56/58/59 were constructed by homology modeling. The final results of the HR HPV L1 modelled in this work showed that in some cases among one and three templates were selected by Phyre2 for proteins modeling as shown in Table 1. The 100% of each model were modelled with a confidence of more than 90%. Further, no region on HPV L1 was modelled by *ab initio* folding simulation since all templates identified and used for models building by Phyre2 belongs to HPV L1 structures reported in PDB.

Table 1. Templates selected by Phyre2 during the HR HPV L1 modeling building.

HR HPV L1 proteins modeled	Code of templates used by Phyre2
HPV 33 L1	1DZL (HPV 16)
HPV 58 L1	2R5K (HPV 11) and 1DZL (HPV 16)
HPV 52 L1	2R5K (HPV 11) and 1DZL (HPV 16)
HPV 31 L1	1DZL (HPV 16)
HPV 39 L1	2R5I (HPV 18) and 1DZL (HPV 16)
HPV 45 L1	1DZL (HPV 16) and 2R5I (HPV 18)
HPV 51 L1	2R5K (HPV 11), 2R5I (HPV 18) and 1DZL (HPV 16)
HPV 56 L1	2R5K (HPV 11), 2R5I (HPV 18) and 1DZL (HPV 16)

HR HPV L1: High Risk Human Papillomavirus L1 protein

Refinement of protein structure models and quality assessment

All the second models refined by GalaxyRefine showed a good improvement of its quality as shown in Table 2. The stereochemical quality of the homology models of HR HPV L1 types 31/33/39/45/51/52/56/58/59 was analyzed using the PROCHECK and RAMPAGE programs. The Ramachandran plot obtained from RAMPAGE uses a new Cbeta measure and updated of it. Both Ramachandran plot analysis revealed that all these models have good stereochemical properties, even before refinement of it. Similarly, the results obtained by ERRAT and PROSA web tool during the assessment of the overall model quality also showed good scores. Generally, all these results are within the range of values typically found for native proteins.

Table 2. Results of the quality for each HPV L1 using different tools, before and after refinement of HPV L1 monomers.

L1 proteins modeled	ERRAT-Overall quality factor	ProSA-web (Z-Score)-Overall model quality	RAMPAGE (Number of residues in favoured region)	PROCHECK (Number of residues in favoured region)
HPV 31 L1	67.401/85.349	-6.35/-6.64	94.5%/97.4%	85.5%/93.5%
HPV 33 L1	66.517/81.860	-6.6/-6.55	94.7%/96.9%	86.8%/93.5%
HPV 39 L1	66.516/89.302	-6.76/-6.45	92.7%/97.4%	85.9%/92.8%
HPV 45 L1	72.727/84.944	-6.22/-6.1	93.7%/96.7%	84.1%/91.4%
HPV 51 L1	64.719/83.900	-6.41/-6.52	94.5%/97.4%	88.6%/92.5%
HPV 52 L1	67.627/90.389	-6.55/-6.54	95.0%/96.9%	85.9%/92.8%
HPV 56 L1	74.715/86.256	-6.41/-6.28	96.0%/97.6%	86.4%/93.7%
HPV 58 L1	65.991/87.298	-6.6/-6.78	95.1%/97.6%	87.5%/94.4%
HPV 59 L1	61.937/85.126	-5.85/-5.83	94.5%/96.5%	86.3%/92.1%

Before refinement: numerical values in **black**

After refinement: numerical values in **red**

Pentamer building and molecular docking

As a main reference in the discussion of the most results obtained in this work, the work done by Dasgupta and coworkers was taken into account (22).

All pentamers determined in this work show on its surface a variable charge distribution, suggesting different binding mode between pentamers and heparin, taking into account that charge-charge interaction for the formation of this complex have been reported (22). These pentamers have a central hole with a highly negative charge density which varies in size in the different HPV types (Figure 2), similar to those reported by Dasgupta and coworkers in their studies on the HPV 16 and HPV 18 pentamers in complex with heparin (22).

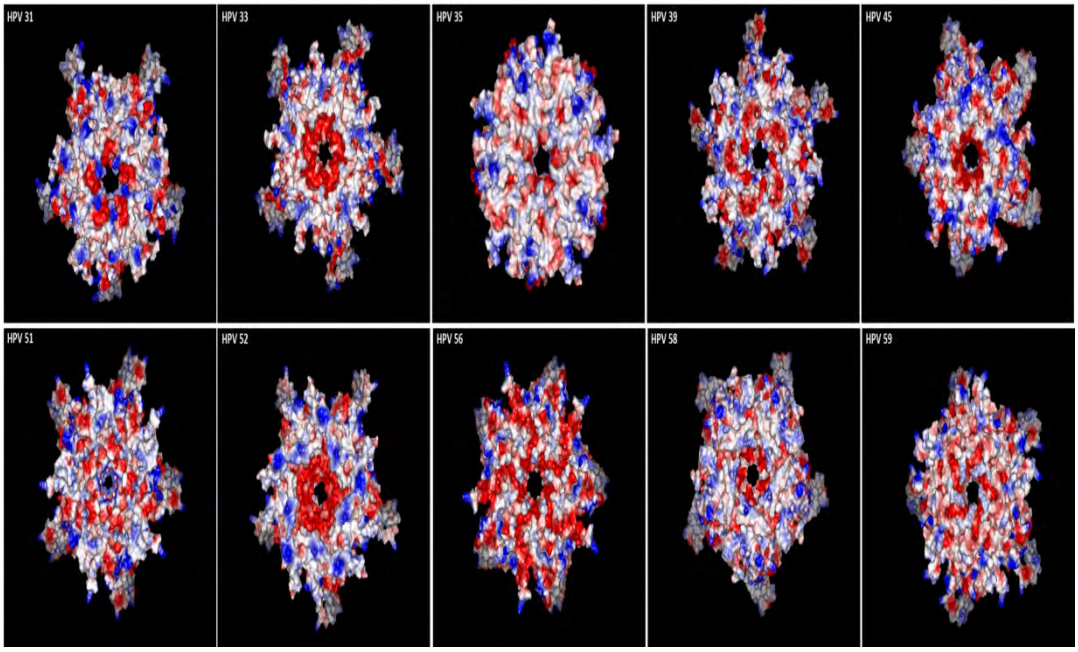

Figure 2. Charge distributions on the surface of the pentamers. Positive charge (Blue) and Negative charge (Red) visualized with the Pymol Molecular Graphics software 1.7.0.1.

As a previous study it was observed that heparin oligosaccharides bind to the monomers surface mainly through charge-charge and polar interactions (22). In this work, it was observed that heparin binding in the loops were located in monomers regions with a positive charge, which could be due to the negative charge of heparin. Moreover, polar interactions were observed (Figure 3).

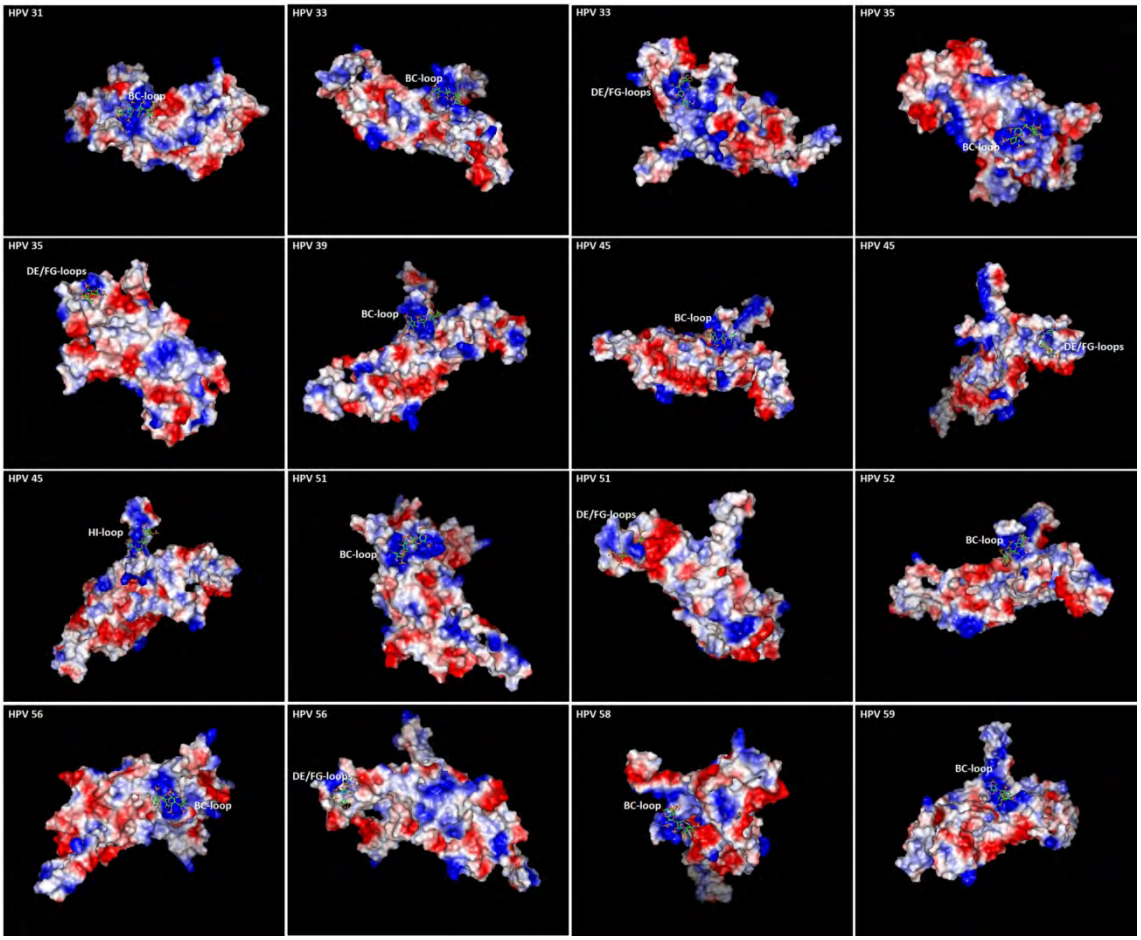

Figure 3. Binding sites of the heparin in the HR HPV L1 monomers through charge-charge interactions. Positive charge (Blue) and Negative charge (Red) visualized with the Pymol Molecular Graphics software 1.7.0.1.

For the HR HPV L1 31/33/35/39/45/51/52/56/58/59, all heparin-binding sites are conformational for each monomer, consisting in residues scattered on more than one surface loop that include in some cases a combination of it. The binding modes for the heparin oligosaccharides in HR HPV L1 types are as shown in (Figure 4) and the residues participating in binding the heparin are as follow: HPV 31 (BC-loop: Lys 41, Lys 35, Asn 38), HPV 33 (BC-loop: Lys 46, Ser 32, Lys 34, Lys 40) (FG-loop Ser 269, Lys 247, Arg 244) (DE-loop Asn 106, Arg 126), HPV 35 (BC-loop Lys 40, Lys 35, Ser 38), (DE-loop Ser 120, Asn 119, Lys 115), (FG-loop Ser 269, Ser 267, Thr 264), HPV 39 (BC-loop Lys 32, Lys 45, Gln 41, Asn 36, Arg 39), HPV 45 (BC-loop Lys 46, Arg 32, Gln 42, Lys 41) (DE-loop Thr 118) (FG-loop Tyr 258, Arg 267, Thr 269, Ser 272) (HI-loop Thr 332, Lys 334, Thr 343), HPV 51 (BC-loop Arg 39, Lys 35, Ser 37,Thr 36) (FG-loop Tyr 272, Asn 242, Tyr 270, Arg 264) (DE-loop Thr 109, Ser 112, Asn 111, Asn 116, Arg 113), HPV 52 (BC-loop Lys 42, Lys 34), HPV 56 (BC-loop Asn 37, Lys 35, Lys 39, Asn 41) (FG-loop Tyr 271, Asn 242, Ser 269, Lys 258, Arg 263) (DE-loop Asn 116, Ser 112), HPV 58 (BC-loop Lys 40, Lys 34, Asn 37), HPV 59 (BC-loop Gln 50, Lys 45, Lys 32, Gln 41). It is worth highlighting that these binding sites may be structured between adjacent monomers which are forming pentamers as reported by Dasgupta and coworkers.

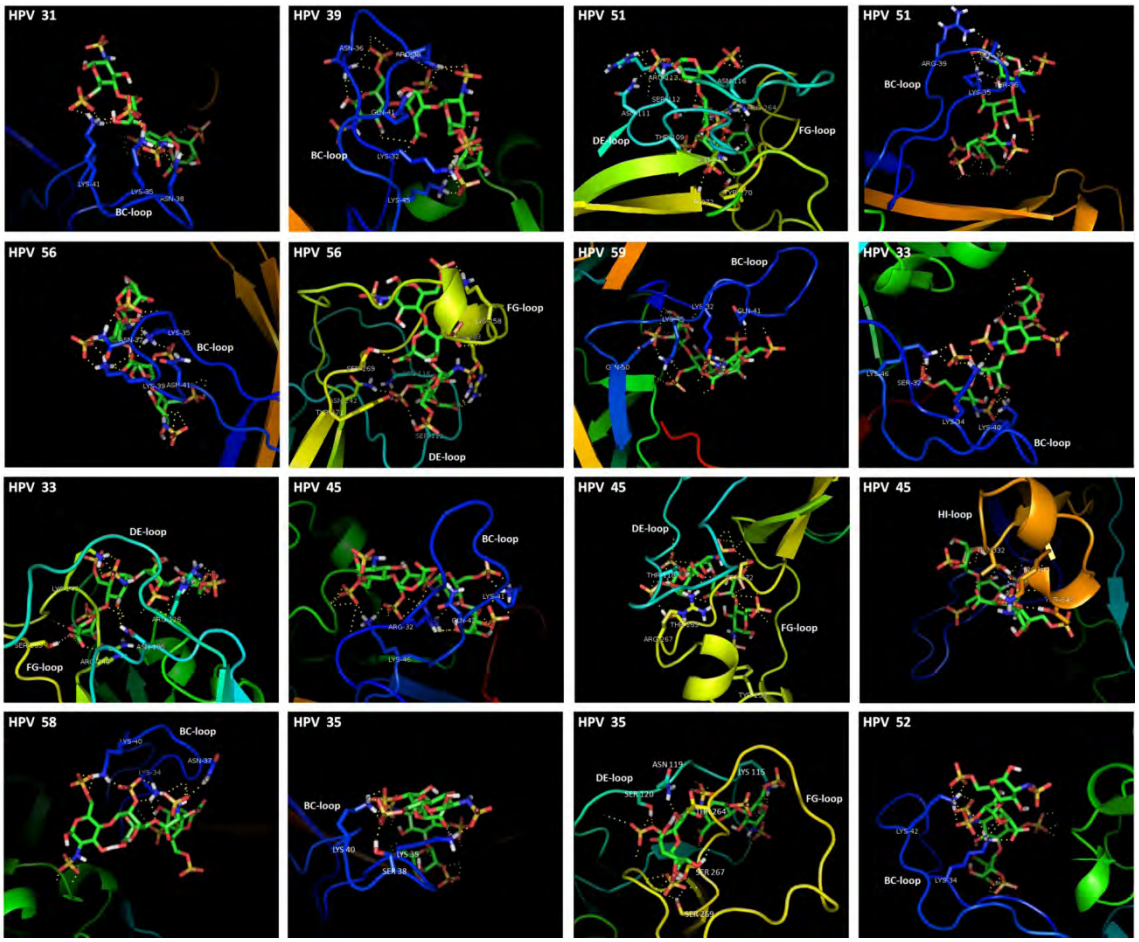

Figure 4. Amino acid residues involves in HR HPV L1-loops interactions. Polar interactions are indicated with yellow dashed lines. All representations are visualized with the Pymol Molecular Graphics software 1.7.0.1.

It was noted the contribution of the BC-loop regions to heparin binding, which is observed in all the HPV L1 monomers. Also it was observed that most of interactions involve the lysine residues, which can be due to the charge-charge interaction between positive charge of lysine and the negative charge of the sulfate groups of heparin. Although not all loops for each HR HPV types are involved in the interaction with heparin, it is remarkable the presence of the BC-loop in all interactions with heparin which could suggest an important common role of this structure during the HR HPV infections.

It is also important to note that the results determined on the docking analysis of the crystal structure of the L1 protein of HPV 35 are similar to those determined from the 3D structures predicted in this study, regarding the number of loops involved in the interaction with heparin, which can be taking into account as benchmark in the analysis of the interactions established among the HR HPV L1 determined by *in silico* methods and heparin.

CONCLUSION

The heparin-binding site in the loops for all the HR HPV reported in this work seems to plays an important role during HR HPV infections that involves heparan sulfate as receptor. Among all loops in the HR HPV L1, BC-loop constitute the most required structure during the HR HPV L1-heparin interactions. Lysine residues are mostly interacting with heparin in some loops, indicating an important role of this residue as stabilizer of such interaction. The charge-charge and polar interactions are the main forces stabilizing the HR HPV L1-heparin. The insight reported in this work related to heparin-HPV L1 interactions are very important for the understanding of HPV immunology and drug designing.

REFERENCES

[1] de Sanjose S, Diaz M, Castellsague X, Clifford G, Bruni L, Munoz N, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. The Lancet infectious diseases. 2007;7(7):453-9. Epub 2007/06/29.

[2] Zanier K, ould M'hamed ould Sidi A, Boulade-Ladame C, Rybin V, Chappelle A, Atkinson A, et al. Solution structure analysis of the HPV16 E6 oncoprotein reveals a self-association mechanism required for E6-mediated degradation of p53. Structure. 2012;20(4):604-17. Epub 2012/04/10.

[3] Doorbar J, Quint W, Banks L, Bravo IG, Stoler M, Broker TR, et al. The biology and life-cycle of human papillomaviruses. Vaccine. 2012;30 Suppl 5:F55-70. Epub 2012/12/05.

[4] Buck CB, Day PM, Trus BL. The papillomavirus major capsid protein L1. Virology. 2013;445(1-2):169-74. Epub 2013/06/27.

[5] Schiller JT, Lowy DR. Understanding and learning from the success of prophylactic human papillomavirus vaccines. Nature reviews Microbiology. 2012;10(10):681-92. Epub 2012/09/11.
[6] Bishop B, Dasgupta J, Klein M, Garcea RL, Christensen ND, Zhao R, et al. Crystal structures of four types of human papillomavirus L1 capsid proteins: understanding the specificity of neutralizing monoclonal antibodies. The Journal of biological chemistry. 2007;282(43):31803-11. Epub 2007/09/07.
[7] Roberts JN, Buck CB, Thompson CD, Kines R, Bernardo M, Choyke PL, et al. Genital transmission of HPV in a mouse model is potentiated by nonoxynol-9 and inhibited by carrageenan. Nature medicine. 2007;13(7):857-61. Epub 2007/07/03.
[8] Horvath CA, Boulet GA, Renoux VM, Delvenne PO, Bogers JP. Mechanisms of cell entry by human papillomaviruses: an overview. Virology journal. 2010;7:11. Epub 2010/01/22.
[9] Roden RB, Kirnbauer R, Jenson AB, Lowy DR, Schiller JT. Interaction of papillomaviruses with the cell surface. Journal of virology. 1994;68(11):7260-6. Epub 1994/11/01.
[10] Muller M, Gissmann L, Cristiano RJ, Sun XY, Frazer IH, Jenson AB, et al. Papillomavirus capsid binding and uptake by cells from different tissues and species. Journal of virology. 1995;69(2):948-54. Epub 1995/02/01.
[11] Volpers C, Unckell F, Schirmacher P, Streeck RE, Sapp M. Binding and internalization of human papillomavirus type 33 virus-like particles by eukaryotic cells. Journal of virology. 1995;69(6):3258-64. Epub 1995/06/01.
[12] Sapp M, Day PM. Structure, attachment and entry of polyoma- and papillomaviruses. Virology. 2009;384(2):400-9. Epub 2009/01/23.
[13] Joyce JG, Tung JS, Przysiecki CT, Cook JC, Lehman ED, Sands JA, et al. The L1 major capsid protein of human papillomavirus type 11 recombinant virus-like particles interacts with heparin and cell-surface glycosaminoglycans on human keratinocytes. The Journal of biological chemistry. 1999;274(9):5810-22. Epub 1999/02/20.
[14] Giroglou T, Florin L, Schafer F, Streeck RE, Sapp M. Human papillomavirus infection requires cell surface heparan sulfate. Journal of virology. 2001;75(3):1565-70. Epub 2001/01/11.
[15] Drobni P, Mistry N, McMillan N, Evander M. Carboxy-fluorescein diacetate, succinimidyl ester labeled papillomavirus virus-like particles fluoresce after internalization and interact with heparan sulfate for binding and entry. Virology. 2003;310(1):163-72. Epub 2003/06/06.
[16] Surviladze Z, Dziduszko A, Ozbun MA. Essential roles for soluble virion-associated heparan sulfonated proteoglycans and growth factors in human papillomavirus infections. PLoS pathogens. 2012;8(2):e1002519. Epub 2012/02/22.
[17] Combita AL, Touze A, Bousarghin L, Sizaret PY, Munoz N, Coursaget P. Gene transfer using human papillomavirus pseudovirions varies according to virus genotype and requires cell surface heparan sulfate. FEMS microbiology letters. 2001;204(1):183-8. Epub 2001/10/30.
[18] Selinka HC, Giroglou T, Sapp M. Analysis of the infectious entry pathway of human papillomavirus type 33 pseudovirions. Virology. 2002;299(2):279-87. Epub 2002/08/31.
[19] Richards KF, Bienkowska-Haba M, Dasgupta J, Chen XS, Sapp M. Multiple heparan sulfate binding site engagements are required for the infectious entry of human papillomavirus type 16. Journal of virology. 2013;87(21):11426-37. Epub 2013/08/24.
[20] Raff AB, Woodham AW, Raff LM, Skeate JG, Yan L, Da Silva DM, et al. The evolving field of human papillomavirus receptor research: a review of binding and entry. Journal of virology. 2013;87(11):6062-72. Epub 2013/03/29.
[21] Cruz L, Meyers C. Differential dependence on host cell glycosaminoglycans for infection of epithelial cells by high-risk HPV types. PloS one. 2013;8(7):e68379. Epub 2013/07/19.
[22] Dasgupta J, Bienkowska-Haba M, Ortega ME, Patel HD, Bodevin S, Spillmann D, et al. Structural basis of oligosaccharide receptor recognition by human papillomavirus. The Journal of biological chemistry. 2011;286(4):2617-24. Epub 2010/12/01.
[23] Khan S, Rodriguez E, Patel R, Gor J, Mulloy B, Perkins SJ. The solution structure of heparan sulfate differs from that of heparin: implications for function. The Journal of biological chemistry. 2011;286(28):24842-54. Epub 2011/05/18.
[24] Edgar RC. MUSCLE: multiple sequence alignment with high accuracy and high throughput. Nucleic acids research. 2004;32(5):1792-7. Epub 2004/03/23.
[25] Edgar RC. MUSCLE: a multiple sequence alignment method with reduced time and space complexity. BMC bioinformatics. 2004;5:113. Epub 2004/08/21.
[26] Chen XS, Garcea RL, Goldberg I, Casini G, Harrison SC. Structure of small virus-like particles assembled from the L1 protein of human papillomavirus 16. Molecular cell. 2000;5(3):557-67. Epub 2000/07/06.
[27] Kelley LA, Sternberg MJ. Protein structure prediction on the Web: a case study using the Phyre server. Nature protocols. 2009;4(3):363-71. Epub 2009/02/28.
[28] Heo L, Park H, Seok C. GalaxyRefine: Protein structure refinement driven by side-chain repacking. Nucleic acids research. 2013;41(Web Server issue):W384-8. Epub 2013/06/06.
[29] Pierce B, Tong W, Weng Z. M-ZDOCK: a grid-based approach for Cn symmetric multimer docking. Bioinformatics. 2005;21(8):1472-8. Epub 2004/12/23.
[30] Laskowski RA, Rullmannn JA, MacArthur MW, Kaptein R, Thornton JM. AQUA and PROCHECK-NMR: programs for checking the quality of protein structures solved by NMR. Journal of biomolecular NMR. 1996;8(4):477-86. Epub 1996/12/01.
[31] Lovell SC, Davis IW, Arendall WB, 3rd, de Bakker PI, Word JM, Prisant MG, et al. Structure validation by Calpha geometry: phi,psi and Cbeta deviation. Proteins. 2003;50(3):437-50. Epub 2003/01/31.
[32] Colovos C, Yeates TO. Verification of protein structures: patterns of nonbonded atomic interactions. Protein science : a publication of the Protein Society. 1993;2(9):1511-9. Epub 1993/09/01.
[33] Wiederstein M, Sippl MJ. ProSA-web: interactive web service for the recognition of errors in three-dimensional structures of proteins. Nucleic acids research. 2007;35(Web Server issue):W407-10. Epub 2007/05/23.
[34] Comeau SR, Gatchell DW, Vajda S, Camacho CJ. ClusPro: an automated docking and discrimination method for the prediction of protein complexes. Bioinformatics. 2004;20(1):45-50. Epub 2003/12/25.
[35] Touze A, Mahe D, El Mehdaoui S, Dupuy C, Combita-Rojas AL, Bousarghin L, et al. The nine C-terminal amino acids of the major capsid protein of the human papillomavirus type 16 are essential for DNA binding and gene transfer capacity. FEMS microbiology letters. 2000;189(1):121-7. Epub 2000/07/29.
[36] Lowe J, Panda D, Rose S, Jensen T, Hughes WA, Tso FY, et al. Evolutionary and structural analyses of alpha-papillomavirus capsid proteins yields novel insights into L2 structure and interaction with L1. Virology journal. 2008;5:150. Epub 2008/12/18.
[37] Bousarghin L, Touze A, Combita-Rojas AL, Coursaget P. Positively charged sequences of human papillomavirus type 16 capsid proteins are sufficient to mediate gene transfer into target cells via the heparan sulfate receptor. The Journal of general virology. 2003;84(Pt 1):157-64. Epub 2003/01/21.