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TLR7 Gene Responses in HIV-Infected Humans vs. Livestock: An In Silico Exploration

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Abstract

The Toll-like receptor 7 (TLR7) is an essential to the immune response against viral infections, mainly HIV. This study examines the amino acid interactions between TLR7 and HIV across three species: humans, cows, and sheep, concentrating on binding distances and docking scores as indicators of interaction strength. In humans, the most favorable interactions include 330A (Lysine, LYS) with 540A (Arginine, ARG) at a distance of 1.642 Å and a docking score of -316.27, indicating strong electrostatic interactions. The second best interaction, 242A (Asparagine, ASN) and 269B (Glutamine, GLN), displays a distance of 2.516 Å, likely involving hydrogen bonding for enhanced specificity. In cattle, the interaction between 561A (Glutamic Acid, GLU) and 1B (Proline, PRO) is remarkably the strongest across species, with a distance of 1.439 Å and a docking score of -235.19. In sheep, the interaction 559A (Glutamine, GLN) with 96B (Histidine, HIS) at 2.181 Å reflects effective binding with a score of -295.91. Generally, these interactions expose critical insights into the structural dynamics of TLR7's recognition of HIV, highlighting the significance of binding affinities in immune response strategies. This analysis can guide the progress of therapeutic approaches to improve TLR7-mediated responses to HIV across various species.

Key words: TLR7, HIV, Immune Response , Amino Acid Interactions , Binding Affinity

الملخص

المستقبل الشبيه بالإنزيم 7 **(TLR7)** يعتبر عنصرًا أساسيًا في الاستجابة المناعية ضد العدوى الفيروسية، وخاصة فيروس نقص المناعة البشرية **(HIV).** تدرس هذه الدراسة تفاعلات الأحماض الأمينية بين **TLR7** و **HIV** عبر ثلاثة أنواع وهي: البشر، الأبقار، والغنم، مع التركيز على مسافات الربط والنقاط المرتبطة كدلائل على قوة التفاعل .

في البشر، تشمل التفاعلات الأكثر ملاءمة **A330** (الليسين، **LYS**) مع **A540** (الأرجينين، **ARG**) على مسافة 1.642 **Å** ودرجة ربط قدرها -316.27، مما يدل على تفاعل كهربائي قوي. أما التفاعل الثاني الأفضل، **A242** (الأسباراجين، **ASN**) و**B269** (الجلوتامين، **GLN**)، فيظهر مسافة 2.516 **Å**، ويحتمل أن ينطوي على روابط هيدروجينية لتعزيز التخصص. في الأبقار، يُعتبر التفاعل بين **A561** (حمض الغلوتاميك، **GLU**) و**B1** (البروتين، **PRO**) هو الأكثر قوة بين الأنواع، حيث تبلغ المسافة 1.439 **Å** ودرجة ربط قدرها -235.19. وفي الغنم، يدل التفاعل **A559** (الجلوتامين، **GLN**) مع **B96** (الهستيدين، **HIS**) عند 2.181 **Å** على ارتباط فعال مع درجة قدرها -295.91. بشكل عام، تكشف هذه التفاعلات عن رؤى حيوية حول الديناميكيات الهيكلية لتعرف **TLR7** على **HIV** مما يبرز أهمية روابط الربط في استراتيجيات الاستجابة المناعية. يمكن أن توجه هذه التحليلات تقدم الأساليب العلاجية لتحسين الاستجابات الوسيطة لـ **TLR7** ضد **HIV** عبر الأنواع المختلفة.

الكلمات المفتاحية : TLR7، **فيروس نقص المناعة البشرية، الاستجابة المناعية، تفاعلات الأحماض الأمينية، قوة الارتباط**

Introduction

The Toll-like receptor 7 (TLR7) is an essential component of the innate immune system, helping as an important sensor for viral pathogens[1, 2]. This receptor identifies single-stranded RNA, a common feature of many viruses, comprising human immunodeficiency virus (HIV)[3, 4]. Understanding the role of TLR7 in the framework of HIV infection not only aids in decoding the complexities of human immune response but also covers the way for potential therapeutic strategies[5, 6].

HIV infection remains a global health crisis, affecting millions and posing major challenges to public health systems. Notwithstanding considerable progressions in understanding

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HIV pathogenesis, effective vaccination strategies and cures remain mysterious[7, 8]. The immune system's capability to detect and respond to viral infections is initial in combating diseases such as HIV. TLR7 has reaped interest due to its role in activating antiviral immune responses, prompting both humoral and cellular immunity[9, 10]. This interest is particularly relevant in the context of HIV, where the immune response can be dysfunctional, leading to chronic infection and disease progression[11, 12].

In humans, TLR7 is predominantly expressed in plasmacytoid dendritic cells and definite lymphatic tissues, enabling the recognition of HIV RNA and subsequent activation of immune responses[13, 14]. When activated, TLR7 leads to the assembly of type I interferons and pro-inflammatory cytokines that are vital for antiviral defense[15, 16]. However, the interaction between TLR7 activation and HIV pathogenesis is complex, as the virus has developed mechanisms to evade immune detection, leading to insistent infection. Understanding how TLR7 functions in this context is critical for evolving effective immunotherapies and vaccines against HIV[17, 18].

Comparatively, the immune responses in livestock—such as cows, pigs, and chickens—focus a compelling area of study. Livestock species have been revealed to display differing TLR7 responses to various pathogens, reflecting evolutionary adaptation to their distinctive environments and the pathogens they encounter. For instance, while some livestock species may have similar homologs of TLR7, the structural variants in these receptors can influence how they recognize viral RNA and initiate immune responses. This raises fascinating questions about the role of TLR7 in livestock during viral infections and how insights from these species can inform our understanding of TLR7 functionality in humans.

The contrasting TLR7 responses between HIV-infected humans and livestock not only light species-specific immune mechanisms but also underline the potential for cross-species insights[10]. By analyzing TLR7 gene variations and responses through these groups, investigators can better understand the evolutionary burdens shaping these immune receptors. Such comparative studies can reveal patterns of immune evasion employed by viruses and the corresponding strategies accepted by different hosts[19].

Moreover, discovering the implications of TLR7 functionality in both humans and livestock covers beyond viral immunity[20]. The understanding increased through such research can inform veterinary practices and develop livestock health management, which is vital for food security and public health[21]. The parallels between human and animal immunology also focus the significance of a One Health approach, where human, animal, and environmental health are unified[22]. This study aims to explore the differences in TLR7 gene response between HIV-infected humans and livestock, offering insights into viral immunity and the evolutionary implications of immune system variability.

Methods

Homology Modeling

The amino acid sequences of Toll-like receptor 7 (TLR7) from *Homo sapiens*, *Bos taurus*, *Ovis aries*, and *Bubalus bubalis* were retrieved from the UniProt database. As crystal structures of these species were not available, homology modeling was performed using the Prime module of Schrödinger Suite 2023-1[23]. Suitable template structures were selected based on sequence identity using BLAST, and models were generated, followed by loop refinement and energy minimization using the OPLS4 force

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field to ensure optimal structural geometry[24].

Viral Protein Structure Preparation

The crystal structures of HIV (PDB ID: **1HQU**) was obtained from the RCSB Protein Data Bank. Structure was prepared using the Protein Preparation Wizard in Maestro by assigning bond orders, optimizing hydrogen bonds, removing steric clashes, and minimizing energy with the OPLS4 force field[25].

Protein–Protein Docking

Protein–protein docking was carried out using the BioLuminate module in Schrödinger, employing the PIPER algorithm[26]. The leucine-rich repeat (LRR) domain of TLR7, which is crucial for single-stranded RNA (ssRNA) recognition[27], was defined as the receptor, while HIV was used as ligand protein. Each docking run produced thousands of poses, and the top-ranking clusters were selected based on docking score and interface quality. The best docking pose was selected for interaction analysis based on energy minimization and visual inspection.

Interaction Analysis

The top-docked complexes were analyzed using Maestro's Protein Interactions module. Residue-residue interactions such as hydrogen bonds, salt bridges, π–π stacking, and hydrophobic interactions were characterized, and interacting residue distances were measured to evaluate biological relevance[28]. Comparative interaction profiling across species was conducted to assess differences in binding affinity and residue conservation that may explain host-specific viral recognition.

Results and Discussion

The Toll-like receptor 7 (TLR7) shows a vital role in the immune response against viral infections, including HIV[13]. Understanding the interactions between TLR7 and HIV can provide insights into the mechanisms of viral recognition and possible therapeutic targets[29]. This analysis emphases on the best amino acid interactions between TLR7 and HIV in humans, cows, and sheep, observing their binding distances and conforming docking scores (binding energies).

In humans, the best three amino acid interactions with TLR7, based on the lowest binding distances, are emphasized, with a docking score of **-316.27**. The first interaction includes **330A (Lysine, LYS)** and **540A (Arginine, ARG)**, with a distance of **1.642 Å**. This short distance shows strong electrostatic or hydrogen bonding interactions, contributing to high stability in the receptor-ligand complex. The second interaction between **242A (Asparagine, ASN)** and **269B (Glutamine, GLN)** displays a binding distance of **2.516 Å** As shown in Table 1 and Figure 1. The interaction between these polar amino acids likely involves hydrogen bonds, increasing the specificity of the binding. Finally, the interaction between **194A (Threonine, THR)** and **449A (Glutamic Acid, GLU)**, with a distance of **2.758 Å**, proposes the possibility of both hydrogen bonding and hydrophilic interactions, indicating a stable complex formation As shown in Table 1 and Figure 1and 2. Together, these interactions demonstrate a robust binding affinity, essential for TLR7's recognition and response to HIV.

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Table 1. Molecular Docking of TLR7 from Different Species with HIV

S.No	Host Species	Docking Partner (HIV)	Binding Energy (HIV, kcal/mol)	Key Interacting Residues (HIV)
1	Human	(1HQU)	-316.27	Lys 330, Asp 242, Thr 194
2	Cow	(1HQU)	-235.19	Glu 561, His 637, Arg 480
3	Sheep	(1HQU)	-295.91	Glu 559, Pro 762, Ise 214

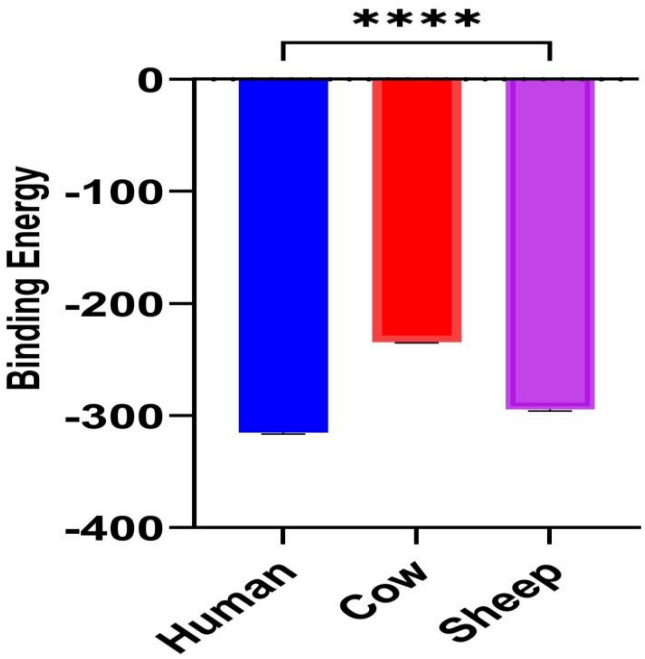

Figure 1. Binding Energy of TLR7 Interactions with HIV Across Species

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This bar graph illustrates the binding energy of TLR7 interactions with HIV in humans, cows, and sheep. The blue bar represents humans, the red bar represents cows, and the purple bar represents sheep. The y-axis indicates the binding energy measured in kcal/mol, with lower values indicating stronger interactions. Statistical analysis shows significant differences (****$p < 0.0001$) in binding energy among the species, highlighting the variation in immune response potential across these mammals. Error bars represent standard deviation.

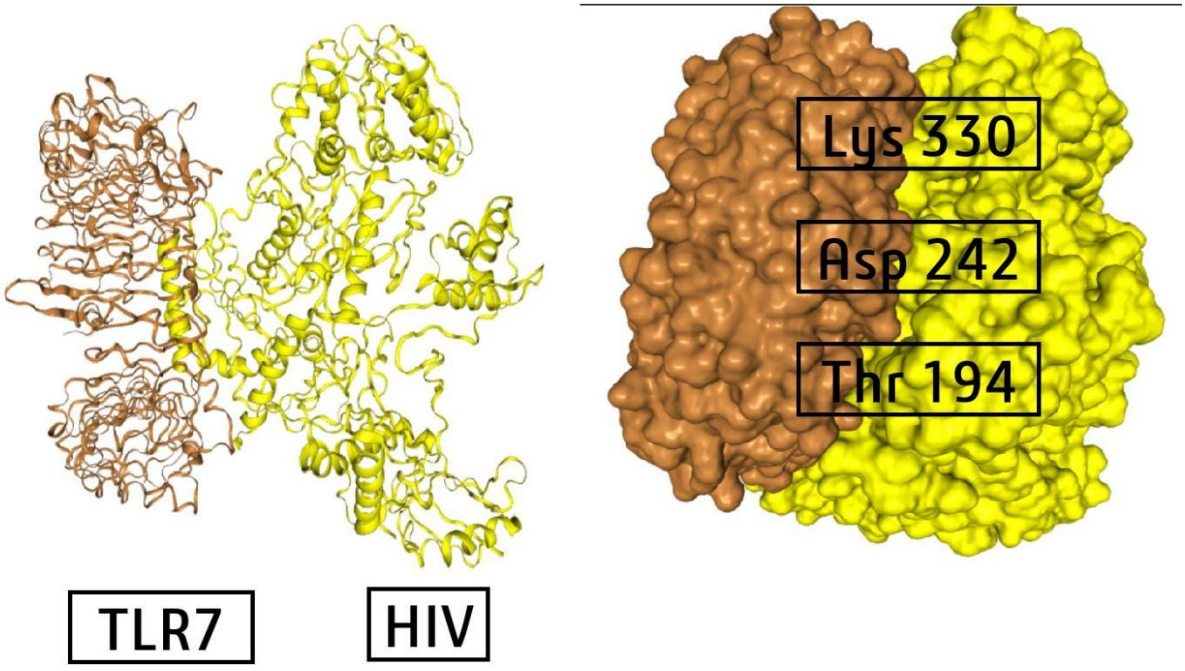

Figure 2. Molecular surface representation of protein–protein docking interactions between human Toll-like receptor 7 (TLR7, yellow) and viral proteins— HIV (Walnut).

In cattle, the top three interactions, with a docking score of **-235.19**, are fairly notable. The first is between **561A (Glutamic Acid, GLU)** and **1B (Proline, PRO)**, which has the shortest distance of **1.439 Å**, making it the strongest interaction across the species observed, suggestive of strong binding stability due to this close vicinity. The second interaction involves **637A (Histidine, HIS)** and **211B (Arginine, ARG)**, with a distance of **1.783 Å**. This communication may include substantial electrostatic interactions that contribute to overall affinity. The third key interaction, between **480A (Arginine, ARG)** and **220B (Lysine, LYS)**, displays a distance of **2.327 Å** As shown in Table 1 and Figure 2 . As basic residues, these amino acids may form salt bridges, providing extra stabilization to the receptor-ligand complex. Notwithstanding the lower docking score compared to humans, these critical amino acid interactions nonetheless facilitate effective viral recognition by TLR7 in cattle.

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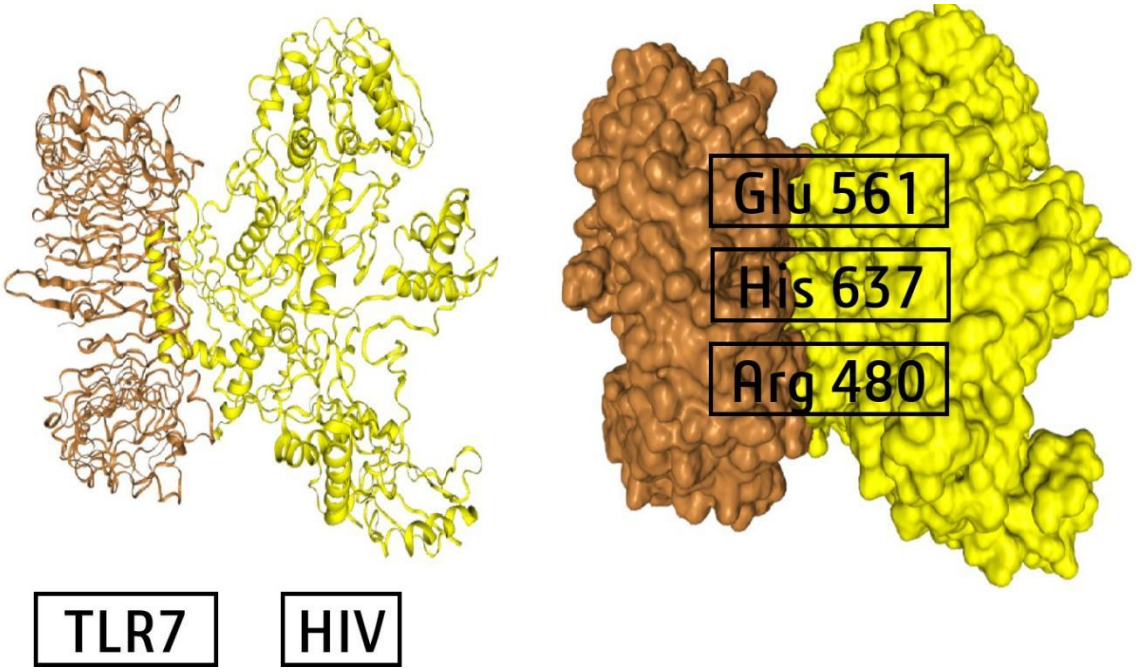

Figure 3. Molecular surface depiction of protein–protein docking interactions between cow Toll-like receptor 7 (TLR7, yellow) and viral proteins— HIV (Walnut)

In sheep, the three best interactions with a docking score of **-295.91** reveal notable affinity as well. The first interaction, which includes **559A (Glutamine, GLN)** and **96B (Histidine, HIS)**, has a distance of **2.181 Å**. This interaction probable includes hydrogen bonding, establishing a stable and specific binding site. The second best interaction is between **762A (Proline, PRO)** and **14B (Proline, PRO)**, with a distance of **2.329 Å**. This interaction proposes a unique compatibility, possibly improving structural integrity within the binding domain. Lastly, the third interaction between **214A (Isoleucine, ILE)** and **449A (Glutamic Acid, GLU)** displays a distance of **2.560 Å** As shown in Table 1 and Figure 3, enabled through a combination of hydrophobic and polar interactions that permit the ligand to fit comfortably within the receptor environment.

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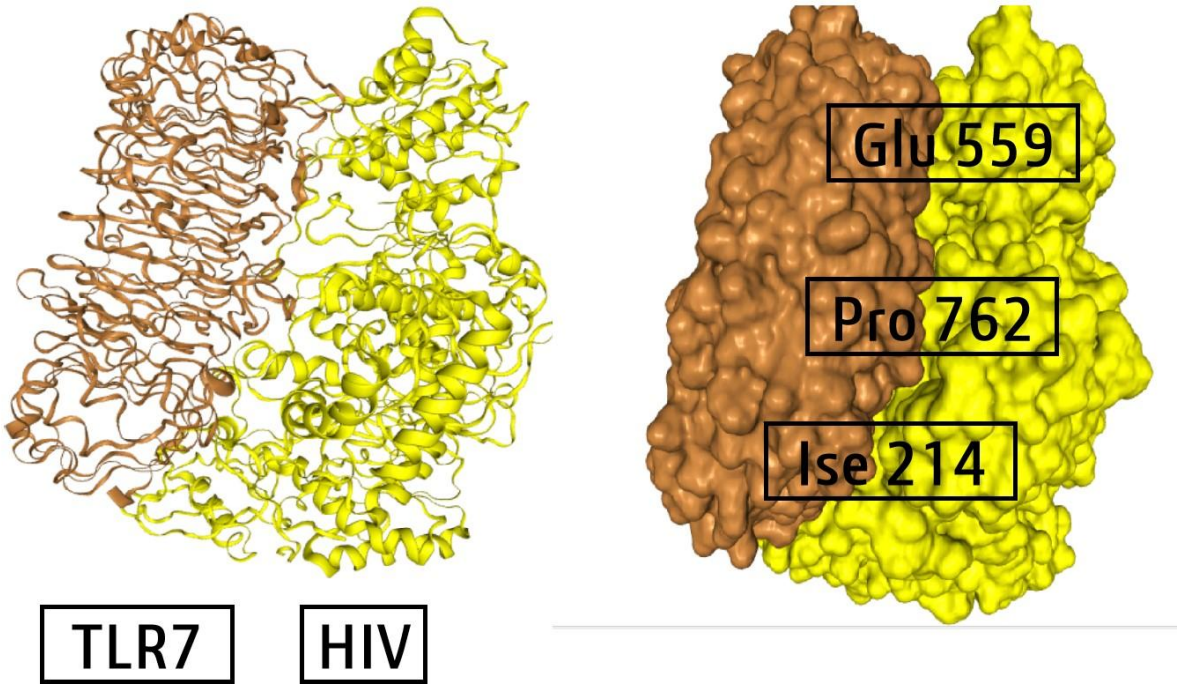

Figure 4. Molecular surface representation of protein–protein docking interactions between Buffalo Toll-like receptor 7 (TLR7, yellow) and viral proteins— HIV (Walnut).

A comparative analysis of TLR7 interactions with HIV reveals that humans have the strongest binding affinity, proved by a docking score of **-316.27** and stable interactions at **1.642 Å**. This indicate the actual efficiency of TLR7 stimulation in human rather than animals may be influenced by various factors, including TLR7 polymorphisms and immune modulators[6, 30].

Conclusion

The comparison of TLR7 interactions with HIV across different species highlights the evolutionary adaptations in immune responses. While the binding energies differ among humans, cows, and sheep, the key interactions are categorized by short binding distances, indicative of strong affinities that are vital for effective immune recognition. The insights gained from this analysis can inform therapeutic strategies aimed at improving TLR7-mediated responses to HIV across species.

References

[1] J. M. Lund *et al.*, "Recognition of single-stranded RNA viruses by Toll-like receptor 7," (in eng), *Proc Natl Acad Sci U S A,* vol. 101, no. 15, pp. 5598-603, Apr 13 2004, doi: 10.1073/pnas.0400937101.

[2] C. Petes, N. Odoardi, and K. Gee, "The Toll for Trafficking: Toll-Like Receptor 7 Delivery to the Endosome," (in English), *Frontiers in Immunology,* Review vol. Volume 8 - 2017, 2017-September-04 2017, doi: 10.3389/fimmu.2017.01075.

[3] Y. van Heuvel, S. Schatz, J. F. Rosengarten, and J. Stitz, "Infectious RNA: Human Immunodeficiency Virus (HIV) Biology, Therapeutic Intervention, and the Quest for a Vaccine," (in eng), *Toxins (Basel),* vol. 14, no. 2, Feb 14 2022, doi:

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ISSN (Print): 2958-8952
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10.3390/toxins14020138.

[4] R. Sartorius, M. Trovato, R. Manco, L. D'Apice, and P. De Berardinis, "Exploiting viral sensing mediated by Toll-like receptors to design innovative vaccines," *npj Vaccines,* vol. 6, no. 1, p. 127, 2021/10/28 2021, doi: 10.1038/s41541-021-00391-8.

[5] M. Rozman, S. Zidovec-Lepej, K. Jambrosic, M. Babić, and I. Drmić Hofman, "Role of TLRs in HIV-1 Infection and Potential of TLR Agonists in HIV-1 Vaccine Development and Treatment Strategies," (in eng), *Pathogens,* vol. 12, no. 1, Jan 5 2023, doi: 10.3390/pathogens12010092.

[6] T. Zhang *et al.*, "Effects of TLR7 Polymorphisms on the Susceptibility and Progression of HIV-1 Infection in Chinese MSM Population," (in eng), *Front Immunol,* vol. 11, p. 589010, 2020, doi: 10.3389/fimmu.2020.589010.

[7] G. Y. Scott and D. Worku, "HIV vaccination: Navigating the path to a transformative breakthrough-A review of current evidence," (in eng), *Health Sci Rep,* vol. 7, no. 9, p. e70089, Sep 2024, doi: 10.1002/hsr2.70089.

[8] E. Kumah, D. S. Boakye, R. Boateng, and E. Agyei, "Advancing the Global Fight Against HIV/Aids: Strategies, Barriers, and the Road to Eradication," (in eng), *Ann Glob Health,* vol. 89, no. 1, p. 83, 2023, doi: 10.5334/aogh.4277.

[9] J. Xue *et al.*, "Unraveled role of TLR7-mediated interferon signaling activation in COVID-19," (in eng), *Front Cell Infect Microbiol* ,vol. 15, p. 1658249, 2025, doi: 10.3389/fcimb.2025.1658249.

[10] A. B. Macedo *et al.*, "Dual TLR2 and TLR7 agonists as HIV latency-reversing agents," (in eng), *JCI Insight,* vol. 3, no. 19, Oct 4 2018, doi: 10.1172/jci.insight.122673.

[11] E. Teer, N. C. Mukonowenzou, and M. F. Essop, "HIV, Inflammation, and Immunometabolism: A Model of the Inflammatory Theory of Disease," (in eng), *Viruses,* vol. 17, no. 6, Jun 11 2025, doi: 10.3390/v17060839.

[12] N. S. Utay and P. W. Hunt, "Role of immune activation in progression to AIDS," (in eng), *Curr Opin HIV AIDS,* vol. 11, no. 2, pp. 131-7, Mar 2016, doi: 10.1097/coh.0000000000000242.

[13] M. E. H. Kayesh, M. Kohara, and K. Tsukiyama-Kohara, "Toll-like Receptor Response to Human Immunodeficiency Virus Type 1 or Co-Infection with Hepatitis B or C Virus: An Overview," (in eng), *Int J Mol Sci,* vol. 24, no. 11, Jun 1 2023, doi: 10.3390/ijms24119624.

[14] O. Manches, D. Frleta, and N. Bhardwaj, "Dendritic cells in progression and pathology of HIV infection," (in eng), *Trends Immunol,* vol. 35, no. 3, pp. 114-22, Mar 2014, doi: 10.1016/j.it.2013.10.003.

[15] J. Di Domizio, A. Blum, M. Gallagher-Gambarelli, J. P. Molens, L. Chaperot, and J. Plumas, "TLR7 stimulation in human plasmacytoid dendritic cells leads to the induction of early IFN-inducible genes in the absence of type I IFN," (in eng), *Blood,* vol. 114, no. 9, pp. 1794-802, Aug 27 2009, doi: 10.1182/blood-2009-04-216770.

[16] T. Duan, Y. Du, C. Xing, H. Y. Wang, and R. F. Wang, "Toll-Like Receptor Signaling and Its Role in Cell-Mediated Immunity," (in eng), *Front Immunol,* vol. 13, p. 812774, 2022, doi: 10.3389/fimmu.2022.812774.

[17] F. Z. Meng *et al.*, "TLR7 Activation of Macrophages by Imiquimod Inhibits HIV Infection through Modulation of Viral Entry Cellular Factors," (in eng), *Biology (Basel),* vol. 10, no. 7, Jul 13 2021, doi: 10.3390/biology10070661.

[18] P. K. Dash, B. D. Kevadiya, H. Su, M. G. Banoub, and H. E. Gendelman, "Pathways towards human immunodeficiency virus

Al-Shatrah Veterinary and Biological Sciences Journal
ISSN (Print): 2958-8952
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elimination," *EBioMedicine,* vol. 53, p. ,2020 /01/03/2020 ,102667doi: https://doi.org/10.1016/j.ebiom.2020.102667.

[19] S. Yoo, K. Youn, N. Kim, G. Keum, H. Park, and E.-K. Bang, "Artificial intelligence-driven discovery of novel scaffolds for selective TLR7 antagonists and their application in enhancing mRNA translation efficiency," *European Journal of Pharmaceutical Sciences,* vol. 212, p. 107172, 2025/09/01/ 2025, doi: https://doi.org/10.1016/j.ejps.2025.107172.

[20] S. N. Lester and K. Li, "Toll-like receptors in antiviral innate immunity) ",in eng), *J Mol Biol,* vol. 426, no. 6, pp. 1246-64, Mar 20 2014, doi: 10.1016/j.jmb.2013.11.024.

[21] C. Ducrot *et al.*, "Animal board invited review: Improving animal health and welfare in the transition of livestock farming systems: Towards social acceptability and sustainability," *animal,* vol. 18, no. 3, p. 101100, 2024/03/01/ 2024, doi: https://doi.org/10.1016/j.animal.2024.101100.

[22] P. Trinh, J. R. Zaneveld, S. Safranek, and P. M. Rabinowitz, "One Health Relationships Between Human, Animal, and Environmental Microbiomes: A Mini-Review," (in eng), *Front Public Health,* vol. 6, p. 235, 2018, doi: 10.3389/fpubh.2018.00235.

[23] A. Waterhouse *et al.*, "SWISS-MODEL: homology modelling of protein structures and complexes," (in eng), *Nucleic Acids Res,* vol ,46 .no. W1, pp. W296-w303, Jul 2 2018, doi: 10.1093/nar/gky427.

[24] G. M. Sastry, M. Adzhigirey, T. Day, R. Annabhimoju, and W. Sherman, "Protein and ligand preparation: parameters, protocols, and influence on virtual screening enrichments," (in eng ,(*J Comput Aided Mol Des,* vol. 27, no. 3, pp. 221-34, Mar 2013, doi: 10.1007/s10822-013-9644-8.

[25] M. P. Jacobson, R. A. Friesner, Z. Xiang, and B. Honig, "On the role of the crystal environment in determining protein side-chain conformations," (in eng ,(*J Mol Biol,* vol. 320, no. 3, pp. 597-608, Jul 12 2002, doi: 10.1016/s0022-2836(02)00470-9.

[26] D. Kozakov *et al.*, "The ClusPro web server for protein-protein docking," (in eng), *Nat Protoc,* vol. 12, no. 2, pp. 255-278, Feb 2017, doi: 10.1038/nprot.2016.1.69

[27] Z. Zhang *et al.*, "Structural Analysis Reveals that Toll-like Receptor 7 Is a Dual Receptor for Guanosine and Single-Stranded RNA," (in eng), *Immunity,* vol. 45, no. 4, pp. 737-748, Oct 18 2016, doi: 10.1016/j.immuni.2016.09.011.

[28] D. Petrey and B. Honig, "GRASP2: visualization, surface properties, and electrostatics of macromolecular structures and sequences," (in eng), *Methods Enzymol,* vol. 374, pp. 492-509, 2003, doi: 10.1016/s0076-6879(03)74021-x.

[29] S. Yadav, V. Verma, R. Singh Dhanda, and M. Yadav, "Insights into the toll-like receptors in sexually transmitted infections," (in eng), *Scand J Immunol,* vol. 93, no. 1, p. e12954, Jan 2021, doi: 10.1111/sji.12954.

[30] Y. Li *et al.*, "Novel TLR7/8 agonists promote activation of HIV-1 latent reservoirs and human T and NK cells," (in eng), *Front Microbiol,* vol. 14, p. 1033448, 2023, doi: 10.3389/fmicb.2023.1033448.