International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 650-655 www.ijprajournal.com ISSN: 2456-4494

A Review on Endogenous Retroviruses as Vaccine Platforms for Emerging Pathogens

Keerthi Thodiyil*
Department of Immunology, Malabar Institute of Medical Science and Research Foundation, Kerala, India
***Address**: Mukkadi Paramb, Puthiyanirath, Elathur PO, Calicut, Kerala- 673303, India,*

Date of Submission: 20-01-2025 Date of Acceptance: 30-01-2025

ABSTRACT:
Remains of long-gone viral infections are integrated in host-genomes, Endogenous retroviruses (ERVs) now serves as a novel platform for the creation of vaccines to combat emerging pathogens. To highlight the immense potential of ERV as a next-generation vaccination platform, this review examines the root causes, advantages and challenges ERVs in vaccine development. Leveraging, viral-like elements including RNA intermediates, and envelope proteins (Env), ERV-based vaccine platforms depend on their intrinsic immunogenicity to recreate the natural viral infections and evoke powerful innate and adaptive immune reactions. Their self-adjuvant peculiarity ease vaccine formulations by eliminating the need for exogenous adjuvants. Preclinical studies on influenza and Zebrafish model have demonstrated that ERVs are diverse in their capability to target various pathogens. However, there are several challenges that ERV-vaccine platforms have to overcome. Some of them are, the likelihood of genomic instability, immunity tolerance and off-target immune reactions. Its developments and applications are further exacerbated by regulatory barriers and production complexity. Despite these challenges, advancements in antigen-design and genetic engineering are continuing to improving the effectiveness and safety of ERV-based vaccinations.

Key words: Endogenous retroviruses (ERVs), envelope proteins, ERV-based vaccine platforms, intrinsic immunogenicity, genomic instability, RNA intermediates

I. INTRODUCTION

Rising infectious diseases (EIDs) involving, Ebola,SARS-CoV-2 and Zikaemphasise thecritical need for innovative vaccine technologies. Live attenuated, inactivated, and subunit-based vaccinations are the maininstances of conventional vaccine techniques that are often laborious and may fail to deliverrapid scalingduring outbreaks of epidemics[1].Consequently, demand for alternative platforms that utilise viral vectors to transport antigens has grown. Of them, endogenous retroviruses (ERVs) have drawn attentiondue to their stability, ability to triggerpowerful immunological responses, and unique incorporation into host genomes[2]. Around 8% of the human genome is comprised of ERVs, which are originated from ancient retroviral infections[3].Exploring the biological features, advantages, and constraints of ERVs, this review discusses their potential as vaccination platforms.

Endogenous Retroviruses: An Overview

As per the studies, ERVs are vestiges of pre-historic retroviral infections that have become ingrained in the genomes of vertebrates and they represent around 8 % of the human genome. These DNA sequences are functionally varied and are passed down across generations. However, throughout evolution, most ERVs underwent deletions and mutations leaving them non-functional[3].Additionally, some express RNA or viral proteins that impact host genome functions. The incorporation of viral genome elements into indispensable physiological procedures is illustrated by the syncytin gene, which is formed from an ERV envelope protein and serves an important role in the development of the syncytiotrophoblast, a multinucleated layer in the placenta in humans and other mammals [4].

From the immunological standpoint, the ERVs are fundamentally immunogenic, as their structural proteins have been shown to tend to trigger innate immune pathways, which include Cytoplasmic RNA sensors and Toll-Like Receptors. Due to this attribute, ERVs have been considered in potential vaccine platforms[5].For instance: in animal models, ERV-derived vectors encoding Ebola glycoproteins have produced potent immune responses, indicating their efficacy in fighting recently developed diseases. Most importantly, there are challenges when employing ERVs. While

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 650-655 www.ijprajournal.com ISSN: 2456-4494

stability is ensured by their genomic incorporation, the evolution of insertional mutations continues to be a cause of concern. In addition, the efficacy of the vaccination might be hindered by pre-existing immunological reactions against the ERV proteins [6]. Regardless of these challenges, advancements in genetic engineering and genome modification offer hope in triumphing across them. From the immunological standpoint, the ERVs are fundamentally immunogenic, as their structural proteins have been shown to tend to trigger innate immune pathways, which include Cytoplasmic RNA sensors (MDA5 andRetinoic acid-inducible gene-I etc) and Toll-Like Receptors (TLR4, TLR3 etc). Due to this attribute, ERVs have been considered in potential vaccine platforms[7]. For instance: in animal models, ERV-derived vectors encoding Ebola glycoproteins have produced potent immune responses, indicating their efficacy in fighting recently developed diseases. Most importantly, there are challenges when employing ERVs. While stability is ensured by their genomic incorporation, the evolution of insertional mutations continues to be a cause of concern[8]. In addition, the efficacy of the vaccination might be hindered by pre-existing immunological reactions in host cells against the ERV proteins. Regardless of these challenges, advancements in genetic engineering and genome modification offer hope in triumphing across them[9].ERVs are an excellent illustration of the way that the evolutionary remnants of previous infections are capable of being novel therapeutic applications, particularly in tackling modern infectious diseases.

Mechanisms and Advantages of ERVs in Vaccine Development

Mechanisms Underpinning ERV Vaccine Platforms

ERV- vaccines depend on retro-viral genomes to express pathogen-derived antigens or to generate virus-like particles (VLPs). Such non-replicating and non-infectious VLPs mirror actual viruses, allowing ERVs to efficiently activate the immune system and imitate real infections. These mechanisms enable them to serve as a vaccination platforms are mainly associated to ERVs responses with innate and adaptive immunity [10]. One of the main aspects of ERVs is their capability to stimulate the pattern recognition receptors (PRRs) in the immune system such as TLRs, RIG-I and MDA-5[11]. In particular, TLR-3 (frequently generate during the viral replication and detects double stranded RNA), and TLR7/8 (a feature shared by retroviruses and targets single stranded RNA) can be activated by the RNA precursors released during the production of ERV-based antigens. These receptormolecules enhance the adjuvant effect of the vaccination and promote the stimulation of antigen-presenting cells (APCs) by mediating the synthesis of Type.1interferons (IFNs) and other pro-inflammatory cytokines. This trait is especially beneficial for developing vaccines targeting infections like Ebola and SARS-CoV-2that requires robust immune responses.[12].

Another important mechanism is the potential of ERVs to develop and express antigens from emerging pathogens. By utilising molecular cloning methods, ERVs can be altered to deliver genes encoding pathogen-specific proteins, particularly glycoproteins. These proteins are synthesised in host cells, processed and expressed on the cell surface along the Major Histocompatibility Complex (MHC) pathways, inducing cytotoxic lymphocytes such as CD4+ helper T cells, CD8+ cytotoxic T cells [13].

Advantages of Endogenous Retroviruses (ERVs) in Vaccine Development

Genomic Stability and Safety

The genetic reliability and security of ERVs as vaccination platforms are one of their foremostadvantages. Because of the genetic mutations that have occurred over millions of years, ERVs are replication-deficient, indicating that they are incapable to replicate by themselves or switch into a pathogenic form [10]. This promises a high degree of biosafety as opposed to live attenuated or replication-competent viral vaccinations. For instance, conventional live vaccines, include the oral polio vaccine, demonstrates the tendency ofvirulence reversions, which in rare instances may end up in vaccine-derived epidemic. As ERV-based vaccines avoid such risk, it makes them safer for immunocompromised people or populations who are vulnerable to adverse effects [14]. Furthermore, ERVs are not prone to horizontal transfer of genes between species, is additionally supported their safety features.

Intrinsic Immunogenicity

Due to the distinctive immunogenic traits, ERVs are considered as promising vaccineplatforms. Theviral-like parts of ERVs such as the envelope protein ERVMER34-1and RNA intermediates mimic natural infections due to the structural and genetic resemblance to functional retroviruses [15]. Due to this similarity, ERVs are capable of interacting effectively with immune

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 650-655 www.ijprajournal.com ISSN: 2456-4494

systems of the host, eliciting innate and adaptive immunological reactions. For instance; ERV-derived RNA can synthesise double-stranded RNA structures (ds-RNA) known to be crucial components of innate immune system[13]. These structures trigger the activate sensory molecules like Retinoic acid-inducible gene I (RIG-I) and Melanoma Differentiation-Associated protein 5 (MDA5). These molecules pertain to the cytosolic PRR family generating to the successive antiviral immunological responses[15].

Moreover, the envelop proteins of ERV, "Env" resembles to those of the exogenous pathogens possess the ability to stimulate the immune cells such as T cells and B cells directly. Since Env proteins boos the antigen presentation mediated by dendritic cells and macrophages that further leads to the activation of T and B cells. A study based on Spring viraemia of carp virus (SVCV) in Zebrafish model identified that Env38, an ERV-derived Env protein, is activated as a part of the adaptive humoral immunogenic responses due to the infection of SVCC). The study explored that that Env38 enhances CD4+T cell activation and promoted the proliferation of IgM^+/IgZ^+ B cell, which helpthe host fight off external viral infection. In particular, Zebrafish IFNφ1 substantially enhanced the expression and activity of Env38, revealing that it performed as an IFN-stimulating gene (ISG), regulated by IFN signalling. Through promoting initial activation of adaptive humoral immunity, this research one of the first studies to discover the role of an Env protein of ERV in hots immunological resistance against an exogenous pathogen [16].

Antigen Presentation of ERV-Derived Proteins

Proteins which act as neoantigens can be synthesisedthrough transcription and translation of ERVs. These neoantigens initiate intracellular processing, and displayed on the cells surfaces with the help of major histocompatibility complex class I (MHC-I) molecules. For CD8+ T cells to identify it and initiate adaptive immunological reactions, this presentation is necessary.After being recognized, these T cellsproliferate and transform into effector cells that can detect and attack cells that express ERV antigens[14]. When ERV expression is higher in certain malignancies, this mechanism has been discovered to leading in spontaneous T cell reactions against tumour cells.For example, MHC-I can exposetumour cells' inactivated ERV proteins, thereby making targets for CTLs[17].

Cost-Effective and Scalable Production

Due to substantial partto theircompliance with widely-recognised cell culture techniques and the opportunityfor high-yield manufacturing methods,ERV-based vaccines promisenovel possibilities for economical and scalable manufacture. ERVs can be alteredto develop vector-based vaccines or VLPs, which may be developed with continuous cell lines like Vero cells. Large-scale productioncan be achieved by the extensiveapplication of these well-characterized cell lines in vaccine manufacturing. Vero cells, for instance, have been established to thrive in high-density cultures and strong growth, both of which are essential for successfullydeveloping viral vectors and VLPs[18].

Furthermore, various antigens can be integrated into ERV-based platforms due to their adaptability, which makes it attainable to design multivalent vaccines without requiringsignificant modifications to the production process. The expense of rearranging manufacturing processes for multiple vaccinations can be reduced by economies of scale achieved about by this versatility. The scalability and cost-efficiency of producing ERV-based vaccines have also been enhanced by advancements in bioprocessing technology, includingthe application of bioreactors and excellent-quality purifying techniques. These innovationsassist in maintaining product consistency and accomplish high yields, both of which are critical for addressing the growing demand for vaccines globally [19].

Challenges in Employing Endogenous Retroviruses (ERVs) for Vaccine Development

While ERV offers unique advantages as vaccination platforms, several issues require to be rectified prior to their full potential can be attained. The challenge of modifying an ancient genetic material for modern immunological purposes appears in these obstacles, that transcend scientific, technical, regulatory and sociocultural domains.Despite the fact that while ERVs are generally appeared be stable, scientific worldis stillconcerned about the unexpected implications of genetic components that are developed from these sequences. For instance: when dormant ERVs are functional during vaccine production, it may causeinadvertent activation of other genetic components or off-target ramifications. As per the studies, ERV sequences have the capacity to interact with surrounding genomic locations and could influence gene expression[20]. This risk must be resolved by careful sequence engineering and

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 650-655 www.ijprajournal.com ISSN: 2456-4494

screening. Studies pointed out that there is a possibility that immune system will not recognise the antigens derived from ERVs, as foreign asERV are integrated into host genome and evolved together with their hosts. This is especially vital when attacking host-like antigens with the help of ERVs. Sophisticated techniques, such modifying ERV sequences to boost their immune responses while maintaining safety must be required to address this challenge. Furthermore, ERV-based vaccine development demands a number of sophisticated procedures. Which includes: optimisation of vector system, batch-to-batch quality checking [21]. For example: meticulous engineering and stringent quality control procedures are essential to ensured that the vectors of ERV-derived vaccination efficiently target antigens while keeping their replication-deficient level[22].In-terms of logistics and technology, it is still challenging to scale these procedures for mass production, particularly, when it comes to rapidly dealing to emerging infectious disease[24]. Although, the advantages of immunogenic nature of ERVs, this feature poses the risk of the activation of off-target immune system. Env proteins and RNA, these are parts of ERVs possess the ability to stimulate non-specific immune pathways, which can end up in the auto-immune reactions or chronic inflammation conditions. For example: renal fibro-inflammation can be elicited by higher ERV levels. The studies exposed that ERV activation caused from the epigenetic inactivation, this induced the inflammatory responses in kidney cells [25]. Similarly, activation of ERV affected the microglial cells, which performs as the predominant immune cells of the central nervous system. As per the study, ERV activation generated microglial inflammatory process, which may suggest an association between ERV activation and neuroinflammatory diseases [26].

Regulatory oversight is made difficult by the innovation of ERV-based vaccine platforms, specificallywith regard to long-term safety. The immunological and genetic complexity of ERVs may not be sufficientlytackled by regulatory frameworks developed for conventional vaccines. Long-term clinical trials and extensive preclinical research are essential to assess potential dangers such genetic variations and off-target effects[27]. One notableexample is the regulatory approval process for vaccines based on adenoviral vectors, which demanded comprehensiveevaluations to ensure a low risk of insertional mutations [28].A framework for overcoming similar issues with ERV-based vaccinations might found in the insights gainedfrom these vaccination platforms.

Future Directions

Overcoming present challenges and reaching full potential of ERV-based vaccines for wider-use will determine its trajectory for the development. Safety and optimization of vector design must be the primary focus. To mitigate the risks of reactivation and off-target repercussions, replication-incompetent ERV clones with accurate genetic modifications should be developed. The creation of ERV-vaccine platforms with greater stability and immunogenicity might be promoted by the breakthroughs in genome-editing techniques such as CRISPR. This method would boost their effectiveness as a vaccine carriers besides assuring safety[29].

The necessity for balanced immunological responses is just as critical. Though ERV-based vaccinations are acknowledged for eliciting strong immune reactions, overstimulating the immune system can causechronic inflammation or autoimmune issues.The practical use of sophisticated adjuvants and regulatory elements that can maintains immune responses must be the top priority in research [30]. Developing vaccines that generate protective immunity without any adverse reactions can be facilitated by systems biology methodologies such as Single-cell RNA sequencing (scRNA-Seq), immune pathway modelling and multi-omics integration, which depict the immunological pathways stimulated by ERVs[31]. By overcoming safety concerns, these attempts would boost the clinical sustainability ofERV-based vaccines.

In addition, governance structures need to evolve to accommodate the specific challenges posed by vaccinations based on ERVs. The immunologic and genetic variability inherent to ERVs may not be properly tackled by present guidelines for traditional vaccinations. Implementing extensive evaluation criteria for preclinical and clinical research demands collaboration between scientists, regulatory bodies, and policymakers. To offer confidence in these ground-breaking vaccine platforms, long-term surveillance procedures must be placed into effect place to examine safety and effectiveness among a wide-range of population [32].

ERV-based vaccines have tremendous potential forcombating autoimmune disorders and cancer as well as infectious diseases. ERV-derived antigens could triggertumour-specific immune responses in cancer immunotherapy, leveraging this

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 650-655 www.ijprajournal.com ISSN: 2456-4494

ability to produce tailored immune reactions. Similarly, such vaccination systems may be explored for autoimmune disease sensitivity induction, offering therapeuticalternatives that are beyond the scopeof traditional methods[33].ERV-based vaccine systems may expand beyond their present limitations and upsurge the scope of their applications in global health by exploring abovementioned areas. To achieve their ground-breaking possibilities, long-term investments in cutting-edge technologies, research, and regulatory modifications will be essential.

II. CONCLUSION

With unique characteristicssuch as inherent immunogenicity, ability in adapting to new infections, and possible for scale production, ERVs offer a novel and intriguing platform for vaccine development. However, its applications also come with substantial challenges, such as concerned about genetic stability, potentiality to create autoimmunity, and insufficiencies in regulatory frameworks. These obstacles can beresolved by progresses in systems biology methods and genome editing techniques like as CRISPR, which can make it possible to effectively construct and modify ERV-based vaccine platforms.

Conflict of interest: No conflict of interest to be disclosed.

REFERENCE

[1]. Aileni M, Rohela GK, Jogam P, Soujanya S, Zhang B. Biotechnological perspectives to combat the COVID-19 pandemic: precise diagnostics and inevitable vaccine paradigms. Cells. 2022 Mar 31;11(7):1182.

[2]. Jarosz AS, Halo JV. Transcription of Endogenous Retroviruses: Broad and Precise Mechanisms of Control. Viruses. 2024 Aug 17;16(8):1312.

[3]. Johnson WE. Origins and evolutionary consequences of ancient endogenous retroviruses. Nature Reviews Microbiology. 2019 Jun;17(6):355-70.

[4]. Roberts RM, Ezashi T, Schulz LC, Sugimoto J, Schust DJ, Khan T, Zhou J. Syncytins expressed in human placental trophoblast. Placenta. 2021 Sep 15;113:8-14.

[5]. Grandi N, Tramontano E. Human Endogenous Retroviruses Are Ancient Acquired Elements Still Shaping Innate Immune Responses. Frontiers in Immunology. 2018 Sep 10;9(2039).

[6]. Imakawa K, Kusama K, Kaneko-Ishino T, Nakagawa S, Kitao K, Miyazawa T, Ishino F. Endogenous retroviruses and placental evolution, development, and diversity. Cells. 2022 Aug 8;11(15):2458

[7]. Li Y, Fan TJ, Cui J. Human endogenous retroviruses in viral disease and therapy. Clinical and translational discovery. 2022 Mar 1;2(1).

[8]. Neukirch L, Fougeroux C, Andersson AM, Holst PJ. The potential of adenoviral vaccine vectors with altered antigen presentation capabilities. Expert review of vaccines. 2020 Jan 2;19(1):25-41.

[9]. Kyriakou E, Magiorkinis G. Interplay between endogenous and exogenous human retroviruses. Trends in Microbiology. 2023 Sep 1;31(9):933-46.

[10]. Wink M, Yousef AE, Carstrom C. An Introduction to Molecular Biotechnology.

[11]. Ogawa H, Honda T. Viral Sequences Are Repurposed for Controlling Antiviral Responses as Non-Retroviral Endogenous Viral Elements. Acta Medica Okayama. 2022;76(5):503-10.

[12]. Browne EP. The role of toll-like receptors in retroviral infection. Microorganisms. 2020 Nov 14;8(11):1787.

[13]. Russ, E. and Iordanskiy, S., 2023. Endogenous retroviruses as modulators of innate immunity. Pathogens, 12(2), p.162.

[14]. ChiscaM, Larouche JD, Xing Q, Kassiotis G. Antibodies against endogenous retroviruses. Immunological Reviews. 2024 Aug 17.

[15]. Sadeq, S., Al-Hashimi, S., Cusack, C.M. and Werner, A., 2021. Endogenous double-stranded RNA. Non-coding RNA, 7(1), p.15.

[16]. Hong Y, Hu CB, Bai J, Fan DD, Lin AF, Xiang LX, Shao JZ. Essential role of an ERV-derived Env38 protein in adaptive humoral immunity against an exogenous SVCV infection in a zebrafish model. PLoS Pathogens. 2023 Apr 4;19(4):e1011222.

[17]. Yu J, Qiu P, Ai J, Liu B, Han GZ, Zhu F, Zhang W, Cui J. Endogenous retrovirus activation: potential for immunology and clinical applications. National science review. 2024 Apr;11(4):nwae034.

[18]. Sène MA, Xia Y, Kamen AA. Overview of recent advances in Vero cells genomic

characterization and engineering for high-throughput vaccine manufacturing. Clinical and Translational Discovery. 2022 Jun;2(2):e40.

[19]. Hamidi A, Hoeksema F, Velthof P, Lemckert A, Gillissen G, Luitjens A, Bines JE, Pullagurla SR, Kumar P, Volkin DB, Joshi SB. Developing a manufacturing process to deliver a cost effective and stable liquid human rotavirus vaccine. Vaccine. 2021 Apr 8;39(15):2048-59.

[20]. Tubbs A, Nussenzweig A. Endogenous DNA damage as a source of genomic instability in cancer. Cell. 2017 Feb 9;168(4):644-56.

[21]. Alcazer V, Bonaventura P, Depil S. Human endogenous retroviruses (HERVs): shaping the innate immune response in cancers. Cancers. 2020 Mar 6;12(3):610.

[22]. Neukirch L, Fougeroux C, Andersson AM, Holst PJ. The potential of adenoviral vaccine vectors with altered antigen presentation capabilities. Expert review of vaccines. 2020 Jan 2;19(1):25-41.

[23]. Bloom DE, Cadarette D. Infectious disease threats in the twenty-first century: strengthening the global response. Frontiers in immunology. 2019 Mar 28;10:549.

[24]. Dhillon P, Mulholland KA, Hu H, Park J, Sheng X, Abedini A, Liu H, Vassalotti A, Wu J, Susztak K. Increased levels of endogenous retroviruses trigger fibroinflammation and play a role in kidney disease development. Nature Communications. 2023 Feb 2;14(1):559.

[25]. Bao H, Yan J, Huang J, Deng W, Zhang C, Liu C, Huang A, Zhang Q, Xiong Y, Wang Q, Wu H. Activation of endogenous retrovirus triggers microglial immuno-inflammation and contributes to negative emotional behaviors in mice with chronic stress. Journal of Neuroinflammation. 2023 Feb 15;20(1):37.

[26]. Chen RT, Shimabukuro TT, Martin DB, Zuber PL, Weibel DM, Sturkenboom M. Enhancing vaccine safety capacity globally: A lifecycle perspective. Vaccine. 2015 Nov 27;33:D46-54.

[27]. David RM, Doherty AT. Viral vectors: the road to reducing genotoxicity. Toxicological Sciences. 2017 Feb 1;155(2):315-25.

[28]. Xue W, Li T, Gu Y, Li S, Xia N. Molecular engineering tools for the development of vaccines against infectious diseases: current status and future directions. Expert Review of Vaccines. 2023 Dec 31;22(1):563-78.

[29]. Rajão DS, Pérez DR. Universal vaccines and vaccine platforms to protect against influenza viruses in humans and agriculture. Frontiers in microbiology. 2018 Feb 6;9:123.

[30]. Gebre MS, Brito LA, Tostanoski LH, Edwards DK, Carfi A, Barouch DH. Novel approaches for vaccine development. Cell. 2021 Mar 18;184(6):1589-603.

[31]. Chavda VP, Bezbaruah R, Valu D, Patel B, Kumar A, Prasad S, Kakoti BB, Kaushik A, Jesawadawala M. Adenoviral vector-based vaccine platform for COVID-19: Current status. Vaccines. 2023 Feb 13;11(2):432.

[32]. Okuyama R. mRNA and Adenoviral Vector Vaccine Platforms Utilized in COVID-19 Vaccines: Technologies, Ecosystem, and Future Directions. Vaccines. 2023 Nov 21;11(12):1737.