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A REVIEW ON EXOSOMES, RELATIONSHIP WITH HIV AND THERAPEUTIC PERSPECTIVES

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Abstract.

As small nanosized particles released from cells by exocytosis, exosomes have been recognized as significant modulators in intercellular communication. Henceforth, it is important to note that these extracellular vesicles may inhibit or enhance viral infection from infected to uninfected ones, thus playing an important role in HIV progression.

Exosomes contain Cargos of protein, mRNA, lipids and other nucleic acids (Jie et al, 2020). Their composition is largely congruent with the cell of origin and the complex biogenesis pathways. Exosomes may contain virus associated nucleic acids and proteins supporting the suggestion that they can transmit infection by ultimately regulating cellular activity which may enhance viral propagation.

However recent exosome studies as far as HIV therapies research is concerned, are focused on regulated synthesis or formation and specific makeup of exosomal content, cell targeting and other non-invasive diagnostic strategies.

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This review article serves to provide more knowledge about exosomes; their biogenesis, composition and relationship with HIV virus. More importantly, we write the therapeutic and diagnostic perspectives contributed by exosomal studies.

Keywords: Exosomes, Biogenesis, HIV.

1. Introduction

The Human immune deficiency virus (HIV) is considered to be one of the deadliest; a cause of the AIDS disease, a noxious pandemic that still affects approximately 36.7-40.5 million people globally as of 2020.

The evolution of HIV can be traced back in the 1930's when the virus was transmitted from chimpanzees and spread to humans. Back then, there was absolutely no cure and any HIV infection would be a straight "death sentence" to the victim.

Thankfully, with advancement in science and technology, ardous research led to discovery of antiretroviral agents (ARV's) such as Zidovudine (the very first of its kind), and later many others in different categories.

It is used in the combinations known as highly active anti-retroviral therapy (HAART), these ARV's contributed great to turning the "death sentence" to a chronic but manageable HIV infection hence increasing patient survival in the long run.

Nevertheless, HAART cannot eliminate the virus from the infected cells, meaning AIDS patients cannot be cured yet. On the top of this, it is reported to be a cause of different co-morbidities and other debilitating side effects to the patients.

Therefore, it is important that continuous research focuses on understanding the latent HIV/HIV reservoir, and possibly its immune system to fight viral infection and disease.

By understanding the various mechanisms behind HIV replication; the factors that the virus thrives to infect cells; all can be a milestone to excellent discoveries.

Recently several studies have shown a correlation between HIV particles and exosomes as closely related. HIV is said to be the first RNA virus to be used for exosome research.

Exosomes are defined as those nano sized vesicular bodies released from cell as ILB's after fusion of MVB's with the plasma membrane.

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With a size diameter of 40-100nm, density 1.13-1.19 g/ml, exosomes are composed of various proteins, RNA, m RNA, t RNA, other nucleic acids and lipids.

However, they should not be confused with apoptotic bodies and ectosomes as these are roughly similar in size as exosomes. Through studies of their biogenesis, analysis, purification and other break through; exosomal research has gained attention especially in its application to HIV novel therapies or diagnosis.

This review study focuses on exosomes, their biogenesis, components, cells that produce then and their relationship with HIV propagation.

Recently, several studies have shown a correlation between the HIV Particle and exosomes as closely related. HIV is said to be the first RNA virus to be used for exosomal research.

Exosomes are defined simply as nanosized vesicular bodies released from a cell at IVB after fusion of MVB with plasma membrane of the cell.

With a size diameter of 40-100nm, density 1.13-1.19g/ml. Exosomes are composed of various proteins, RNA like mRNA, lnRNA, Lipids and other nucleic acids.

However, they should not be confused with apoptotic bodies and ectosome's as these are of roughly similar size.

2. Design/Methods/Modelling

Through studies of their biogenesis, analysis, purification and other breakthroughs exosomal research has gained attention especially in its application to HIV novel therapies or diagnosis.

This review study focuses on exosomes their biogenesis, components and cells that produce them and also the exosome relationship with HIV Propagation.

Exosomes and their Formation:

Formed as a result of physiological or pathological cell condition, exosomes are those cellular vesicles derived from the cell and get out by exocytosis.

They were first discovered in sheep reticulocytes by Johnston et.al.

They are produced by multiple cells including B and T lymphocytes, macrophages, astrocytes, microglia, myoytes, adipocytes among others (Lenassi et.al 2010).

They are found in body fluids that is blood, urine, semen, breast milk.

Exosome diameter is 100-150nm and density is 1.08-1.19g/ml.

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Exosome Biogenesis:

Exosome formation begins with plasma membrane invagination to form endosomes. The endosomes mature into multi vesicular bodies. Further invagination of MVB forms intraluminal vesicles (ILV). This invagination into MVB comes along with incorporation of the cell, cytosolic components, accounting for exosomal composition (as will be mentioned later below).

Exosomal biogenesis is said to happen to occur by two mechanisms i.e., ESCRT-dependent and ESCRT-independent.

According to the ESCRT dependent mechanism endosomal sorting complex required for transport (ESCRT) machinery is employed. This involves ESCRT protein complex 0, I, II, III; ESCRT –O recognizes and aggregates ubiquitinated proteins to specific domains of the endosomal membrane. ESCRT I is then recruited, it merges with ESCRT 2 promote budding off of endosomal membrane to form MVB. Finally ESCRT 3 is recruited to enhance the separating of the vesicle off. The associated proteins involved includeVPS4, Tsg101 and Alix.

ESCRT independent mechanism on the other hand is lipid mediated. It involves lipids and associated protein such as tetraspannin binglin et.al. This process depends on self organization of lipid and cargo domains. This mechanism is not yet well understood.

In exosome biogenesis, the ESCRT dependent mechanism appears to be the most accepted. However, the possibility of ILV to be still formed in absence of ESCRT's supports the thought that there are other different other mechanism though not yet clearly elucidated.

Exosomes Composition:

Alix and TSG101 are proteins involved in exosome formation and release.

Exosome major components are proteins, lipids and nucleic acids, especially the various kinds of RNA. Composition and complexity is extensively diverse as different cells may have various components and in addition to biogenesis pathway complexity.

The proteins with which exosomes are enriched are mainly tetraspannin (CD9, CD63, CD81, CD82) Zhang et.al,2019). These could be contained in exosomes along with Alix, TSG101(proteins involved in exosome release), a together with annexins and Rab (proteins responsible for membrane transport and fusion).

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In addition to proteins, exosomes contain various RNA's also incorporated in them. Several studies have proved microRNA(miRNA)to be the most abundant RNA in exosomes ;rRNA , long non-coding RNA (lnRNA) ,tRNA among others also exist in exosomes in varying propagation.

Lipids present in exosomes are mainly those resulting in formation of ILV following the invagination of MVB hence, these are congruent with those the plasma membrane and hence MVB membrane is made up of such lipids include sphingomyelin, phosphatidylcholine and BMP.

Distinction of Exosome from other Extracellular Vesicles

As already stated in the introduction, exosomes being focused on are unique much as they too are extracellular vesicles.

Extracellular vesicles include exosomes, microvesicles (ectosomes)and apoptotic bodies.

Ideally, complete separation and purification of exosomes from these is arduous, the explanation of which is out of scope of this writing.

Nevertheless, the presence of exosome associated including TSG101, Alix, integrins and tetraspanins (CD9, CD63, CD81) accounts for the uniqueness of exosomes from the other extracellular vesicles (International society for extracellular vesicles).

Exosomes/HIV Relationship

It has been observed that HIV requires ESCRT machinery, just like exosomes for its budding off. The complex interaction of ESCRT complexes with the HIV particles including Gag, Pol and ENV proteins, together with TSG101 ultimately leads to virus budding off. This is hence seen to be similar mechanism to exosome biogenesis.

In addition to this, on a morphological perspective, HIV-1 density 1.16-1.18 g/l and diameter 100-150nm, a closely similar to exosome size, density plus composition.

This overlapping tendency of the two (in their features, size, composition, and biogenesis) complicates things as far as complete separation and purification of exosome is concerned.

Even so, exosomes are metabolically inert and do not replicate, as opposed to HIV-1.

Role of Exosomes in HIV Progression

Remember, exosomes are carriers of cellular material (i.e., nucleic acids, proteins and lipids). Therefore .it should be noted that exosomes are capable of facilitating or inhibiting HIV1 infection. This largely is influenced by the cells from which the exosomes are produced.

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Exosomes, especially those derived from monocytes and macrophages transfer co-receptors (CCR 5 and CXCR4) to cells, hence increasing risk of HIV attack.

They also carry apoptotic agents that lead to macrophage and T cell apoptosis. There may be derived from virus or host cell.

HIV related proteins like Nef, Gag can be transferred to recipient cells by exosomes (Rezaie et.al,2021). These proteins are capable of activating the latent HIV in the cell reservoir, increasing the risk of infection.

Mahajan et.al noted that HIV proteins and exosomes subsequently has an effect on CNS cells and hence a contributor to HIV Associated Neurocognitive Disorder (HAND)

In Preventing / Inhibiting of HIV Infection

Exosomes have shown to delivery antiviral agents; these could be in form of factors necessary for viral protection (antiviral factors)

Promoting HIV transcriptional silencing. This is through disruption of Tat pathway.

Also, exosome compete with host cell to bind envelope protein.

These all inhibit HIV replication, making exosome study an essential application in developing antiretroviral therapy for HIV treatment.

Therapeutic Perspectives of HIV in Relation To Exosome Application

The reason why HIV can't be cured yet is because even ART's cannot wipe it out from the 'reservoirs'. These are called so because they contain the latent HIV, when an activation (perhaps due to stoppage discontinuing of ART by patient) would result in viral replication once again leading to viral rebound and attack to more T-lymphocytes.

Reservoirs are created as soon as HIV infects the cells in lymphoid tissues.

Tireless efforts are currently ongoing to devise means of eliminating the latent HIV which and out which numerous suggestions have come up which are being investigated.

Suggestions stated include:-

-Shock and kill approach:- Activating the latent HIV in infected cells for recognition by antibodies.

-Block and lock approach:- blocking transcription of the virus in reservoirs.

-CRISPR:- gene editing to remove the integrated viral genome.

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Generally, the transfer ability of exosomes is exploited for therapeutic potentials; Since exosomes transport HIV proteins and nucleic acids, they may be thought to trigger transcription on contact with a cell containing latent HIV.

On top of that, they can be packaged with cargos of choice to avail therapies. These have been several studies carried out to target HIV infected cells in order to establish a 'block and lock' of viral expression.

Surya et.al demonstrated that cellular machinery can be engineered to package and deliver recombinant ZPAMT to target the epigenetic silencing of HIV and induce and block and lock phenotype in virus infected cells.

Yong et.al further stressed the therapeutic potential of RNA-based Anti-HIV gene therapies by elaborating on how RNA molecules, a single stranded can be incorporated into exosomes to target complementary HIV RNA in target cells. This would result in degradation of the hybrid double-stranded mRNA /RNA hence inhibiting target gene expression to block ribosome binding. In this case, latent HIV would be block from replication, preventing infection.

Exosomes as Biomakers for HIV Diagnosis

From the variety of body fluids in which exosomes have been discovered (such as urine, blood, saliva, breast milk, semen), exosomes could avail quick and fast diagnosis of HIV.

Plasma exosomes from HIV1 positive patients can be studied for Oxidative stress level maskers, anti-inflammatory Poly Unsaturated Fatty Acids (PUFA), inflammatory regulators etc, in comparison with HIV negative counter parts.

Also, exosome abundance in correlation with CD8 and CD4 T-cells count can be thought of as one other diagnostic way since exosomes are produced often with these cells and other cells always targeted by HIV.

3. Conclusions

Exosomes are formed by a complex pathway within cells; they contain cargos and protein, RNA (miRNA, lncRNA), and lipids.

Exosomes are major players in intercellular communication (cell content transfer/transport) and therefore, they may either inhibit or promote HIV infection.

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Nonetheless, anti-HIV exosomes showing promising have potential to be engaged in clinical trials and along with the incumbent HAART could make an effective regiment against HIV; These anti HIV exosomes are still being investigated through studies involves exosomal packaging of Anti-HIV drugs.

References:

1. Centers for Disease Control and Prevention. Diagnoses of HIV infection in the United States and dependent areas, 2016, vol. 28. 2017.

2. World Health Organization. HIV Drug Resistance Report 2017. Licence: CC BY-NC-SA 3.0 IGO.

3. Alford K, Vera JH. Cognitive impairment in people living with HIV in the ART era: a review. Brit Med Bull. 2018;127:55–68.

4. Anyanwu SI, et al. Detection of HIV-1 and human proteins in urinary extracellular vesicles from HIV+ patients. Adv Virol. 2018;2018:7863412.

5. Arakelyan A, et al. Extracellular vesicles carry HIV Env and facilitate HIV infection of human lymphoid tissue. Sci Rep. 2017;7(1):1695.

6. Armstrong D, Wildman DE. Extracellular vesicles and the promise of continuous liquid biopsies. J Pathol Transl Med. 2018;52(1):1–8.

7. Arts EJ, Hazuda DJ. HIV-1 antiretroviral drug therapy. Cold Spring Harb Perspect Med. 2012;2(4):a007161.

8. Asai H, et al. Depletion of microglia and inhibition of exosome synthesis halt tau propagation. Nat Neurosci. 2015;18(11):1584–93.

9. Barclay RA, et al. Exosomes from uninfected cells activate transcription of latent HIV-1. J Biol Chem. 2017;292(28):11682–701.

10. Carvalhal A, et al. Central nervous system penetration efectiveness of antiretroviral drugs and neuropsychological impairment in the Ontario HIV Treatment Network Cohort Study. J Neurovirol. 2016;22(3):349–57.

11.Cicero AL, Stahl PD, Raposo G. Extracellular vesicles shuffling intercellular messages: for good or for bad. Curr Opin Cell Biol. 2015;35:69–77.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 8, Issue 4, 2019

12. Cihlar T, Fordyce M. Current status and prospects of HIV treatment. Curr Opin Virol. 2016;18:50–6

13. de Jong OG, et al. Cellular stress conditions are refected in the protein and RNA content of endothelial cell-derived exosomes. J Extracell Vesicles. 2012. https://doi.org/10.3402/jev.v1i0.18396.

14. Ensoli B, et al. Tat protein of HIV-1 stimulates growth of cells derived from Kaposi's sarcoma lesions of AIDS patients. Nature. 1990;345(6270):84–6.

15. Fujii Y, et al. Soluble Nef antigen of HIV-1 is cytotoxic for human CD4+ T cells. FEBS Lett. 1996;393(1):93–6.