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Development of Nanotechnology-Based Therapeutic Approaches to Treat HIV

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ABSTRACT
The nanotechnology field is rapidly expanding which involves the synthesis and formulation of materials or small particles which has the least dimensions in nanometers. These nanoparticles are unique in physiochemical properties. Nanoparticles are capable of entering the cellular compartments that explore the specific treatment tactics for life-threatening diseases like AIDS. When the biological systems come into contact with the nano-particles, the physiochemical properties influence the nature of the interactions between the nanoparticles and the biological systems. There are many nanotechnological - based therapies to treat HIV. Antiretroviral therapy helped in decreasing HIV/AIDS mortality. Anti-retroviral drugs are metabolized by the enzyme cytochrome P450. When the CYP substrates are used in the HIV treatment, they have limitations like changes in the drug-drug interactions, low systemic bioavailability, and short half-lives.HIV patients are exposed to adverse effects due to the long-term use of antiretroviral substrates. Through nanocarriers, many antiretroviral agents have been successfully incorporated. The gold nanoparticles are used to deliver mutant caspase-3 selectively to CD4 or infected cells, which leads to morphological changes and induces autophagy. Due to the induction of autophagy, viral production is decreased in HIV-1 infected cells. The formulation of vaginal microbicides through nanotechnology has been investigated about the usage of nanosphere which is capable of reducing HIV-1 infections. In this review, it has been discussed about the concepts of nanotechnology and how nano-pharmaceuticals like nano-carriers, nanoparticles, solid lipid nanoparticles, nanocapsules, micelles, etc exist as budding anti-HIV therapies.
KEYWORDS: *Autophagy, Anti-retroviral drugs, nano-pharmaceuticals, caspase-3, cytochrome P450.*

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INTRODUCTION

Sexually transmitted diseases are concerned globally as they cause /opportunistic infections, infertility even mortality. Among the pathogens like bacteria, viruses, and parasites that are transmitted sexually, the human immunodeficiency virus (HIV) is also one of the most crucial pandemic diseases which cause acquired immunodeficiency syndrome (AIDS) [1]. The causative agent of AIDS is HIV which was identified in 1983. The main target of HIV is the immune system that weakens people's defense against many infections. Beyond the shadow of a doubt, it is essential to know the knowledge about the process of transmission, and the pathogenesis of HIV infection which provides us the important awareness towards developing new and better treatment methods, and also provide the researchers with important opportunities for developing new techniques in preventative measures [2].

THE VIRUS:

The human immunodeficiency virus belongs to the group *Lentivirus* within the *Retroviridae* family. HIV is classified into two types.HIV-1 and HIV-2[3]. Almost all cases of AIDS are caused by HIV-1 globally.HIV-2 causes an AIDS-like illness[4]. The genome of HIV-1 has two single-stranded RNA which are identical. The RNA molecule is enclosed within the core of the viral particle[3]. There are three structural genes in the RNA molecule, that code for group-specific antigens and viral enzymes like reverse transcriptase, integrase, protease, and two glycoproteins in the outer membrane of the virus. The gp120 and gp4 are capable of recognizing the receptor of CD4cells of the host [2].

HIV- HOST CELL INTERACTIONS:

The cell surface proteins CD4 of host cells human cells may be effectively infected by HIV. For infecting the target cell, the HIV needs attachment of human cell through gp120 followed by conformational changes. The virus is fused with the human cell through gp41. After the viral fusion the RNA molecule, reverse transcriptase, and integrase which are present inside the viral core are released into the cytoplasm of human cells. The disassembly of the viral core takes place and the viral RNA is reverse transcribed into DNA through the reverse transcriptase. The reverse-transcribed DNA is migrated into the nucleus of the host cell, where it is inserted into the host chromosomal DNA by the viral enzyme integrase. At this stage, the host cell is now capable of producing virions[2].

HIV TRANSMISSION:

HIV can be transmitted through sexual contact, direct contact of body fluids like blood, semen of an infected person. It is also transmitted from a mother to child during pregnancy [4]. Mostly viral infections occur through the inner foreskin, the penile urethra, which is covered with poor keratinized thin squamous epithelium. The primary carriers of HIV are HIV-infected macrophages present in the vaginal lumen which were infected during sexual intercourse. The immune populations like macrophages, dendritic cells, B-cells, and T-cells in the genital mucosa are mainly susceptible to HIV. The dendritic cells are capable of binding the HIV without membrane fusion that transmits the virus to the secondary lymphoid organs[2].

HIV PATHOGENESIS:

Pathogenesis leads to host immunodeficiency[5].The pathogenesis of HIV-1 infection depends upon the properties of the viruses and the immune response of the host to the viruses. The HIV-infected cells are transmitted to the local immune cells like macrophages,-cells, etc. as well as in the lining of vaginal or anorectal mucosae. The dendritic cell and CD4+ lymphocytes are infected in the cervix mucosa at first. Then the viruses are spread to the lymph nodes and then into the bloodstream. Due to the HIV infection, the lymph nodes function is distorted. The cellular and humoral immune responses are impaired which leads to the weakened capability of the infected host to expand the populations of T-cells and functional memory cells. The circulating CD4+ cells are depleted. Opportunistic infections that define AIDS reflect the impairments in cellular and humoral immune responses[6].

CURRENT TREATMENTS:

The highly active antiretroviral therapy(HAART) was introduced in the1990s which involves the use of a combination of drugs. The use of HAART increased the life expectancy shifting AIDS from acute to chronic disease. To treat HIV infections there are around 30 individual drugs available. Currently, antiretroviral drugs such as reverse transcriptase inhibitors, protease inhibitors, entry inhibitors, and integrase inhibitors are available. The current therapies do not provide a solution for curing HIV due to the ability Of HIV to remain in latency in a cellular and anatomical reservoir. The most common failure of antiretroviral treatment is drug resistance,drug-drug interactions, adverse effects in patients[2]. The technology revolution in pharmaceutical drug delivery is represented by nanotechnology. The basic concept is that nanotechnology helps in targeting the anti-retroviral drugs to particular sites through nanocarriers. When the anti-HIV drugs are enclosed within nanocarriers, it could modify the tissue distribution by targeting the drugs to the HIV reservoir and it also increases the absorption, distribution, and metabolism of the antiretroviral drugs[7].

METHODS

Because of the nanosize, the behavior of the nanoparticle is different from that of the conventional drugs. Dendrimers, liposomes, nanoparticles, niosomes, polymeric micelles,etc are the currently used nanotechnological methods for delivering drugs.

DENDRIMERS

A dendrimer is a polymeric nanostructure made up of small branching units which have an interior and periphery end group, called dendrons. It is arranged layer by layer according to the microenvironment within it. They contain space inside the Dendron which can be used for entrapment of the drug and the protection against degradation from the surrounding environment for targeted drug release. The size of the dendrimer is less than 100nm with 3-dimensional architecture[8].

DELIVERY MECHANISM OF DENDRIMERS

Physically the drug is trapped within the space between the branches. The establishment of the electrostatic force of attraction between the drug and the dendrimer leads to the formation of multiple bonds in the periphery. Now, through the covalent bonds the drugs and the other moieties are attached to the dendrimer that tags the antiretroviral drugs which are attached to the HIV. The other ligands such as antibodies are also covalently bounded. This increases the stability of the drug against degradation, and also improves the therapeutic efficiency [9].

LIPOSOMES

The first type of nanomaterial which was functionalized in drug delivery was liposomes. The liposomes are the spherical structures that are self-assembling composed of amphiphilic phospholipid bilayers that surround the aqueous space in the center. This unique technology is used for delivering the antiretroviral in the macrophage [10].

DELIVERY MECHANISM OF LIPOSOMES

The liposomes are encapsulated with hydrophilic drugs that are localized in organs such as the liver, spleen, and lungs where more macrophages are populated. They are even encapsulated with soluble recombinant CD4 molecule which targets the gp120 of the HIV -infected cells [11].

NANOPARTICLES:

Nanoparticles are solid. They are polymeric particles that are biocompatible. The size of the nanoparticles ranges from 1-100nm. They have an interfacial layer that consists of ions, organic, and inorganic molecules[12]. The nanoparticles are small-sized with a large surface area that are capable of crossing the blood-brain barrier, pulmonary system through the narrow junctions of endothelial cells of the epithelial tissues of the skin[12].

SILVER NANOPARTICLES:

The silver nanoparticles act as an antimicrobial against both gram-negative and gram-positive bacteria, and antiviral agent against HIV-1 virus. This also acts as an entry inhibitor of the HIV-1 virus [13].The anti-HIV activity is exerted by the silver nanoparticles during the early stage of viral replication. It acts as a virucidal agent or as a viral-entry inhibitor. These nanoparticles prevent the post-entry life cycle stages of the HIV-1 virus. The silver nanoparticles bind to the gp-120 of the HIV-1 virus leads to the prevention of the virus fusion between CD4 and the virus[14].

GOLD NANOPARTICLES:

The HIV-1 protease produced by the HIV-infected cells is responsible for the production of infectious virions.HIV- 1 protease activates caspase -3, an enzyme responsible for apoptosis. A mutant form of HIV-1 protease is produced. This mutant form is cleavable only by HIV-1 protease. Gold nanoparticles are used for delivering mutant caspase-3 to CD4+ cells that mimic the HIV infection. Mutant caspase-3 is targeted to the cells that express HIV-1 protease and to the infected CD4+ cells. Infected cells exhibit cellular morphology which leads to autophagy. The induction of autophagy decreases the viral production in HIV-1 infected CD4+ cells. Drugs or antibiotics are conjugated with AUNPs through covalent or ionic bonding or even by physical absorptions[15]. The gold nanoparticles are biologically inactive and are weakly binding particles. The inactive gold nanoparticle is transformed into a multivalent binding particle which inhibits the HIV-1 fusion to human cells. The gold nanoparticles are employed with mercaptobenzoic acid and then are linked to proteins and dendrimers [16]. The poly-anionic characteristics of AUNPs exhibit the anti-HIV activities against HIV-1. Due to this, it binds with the positively charged amino acids at the binding position of gp120. The inhibition mechanism of AUNPs blocks the reverse transcriptase enzyme of HIV-1[17].

POLYMERIC MICELLES

The polymeric micelles are the nanostructures that are formed by the combination of co-polymeric amphiphiles. The copolymers comprise hydrophilic and hydrophobic blocks. The mechanism of polymeric micelles depends upon the block arrangement and the chemical nature of the blocks [18]. The polymeric micelles circulate for a prolonged period and erupt from the vascular system for delivering the drugs to the targeted site of HIV-infections[19].The polymeric micelles are the nanocarriers that comprise an inner hydrophobic core, which traps the poorly-water soluble drugs, and an outer hydrophilic shell in which encapsulated drugs are trapped from the external medium. The outer hydrophilic shell is functionalized with moieties such as folate, monoclonal antibodies, monosaccharides such as mannose, glucose, fructose which can achieve active targeting. The block copolymers are used as a drug delivery vehicle in the polymeric micelles. The block copolymers are made up of derivatives of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) which are mostly used amphiphilic materials. The block copolymers exhibit less stable formulations so that the micelles dissociate easily when it is exposed to the bloodstream[20].

BUKKY BALLS

The fullerene molecules are the allotropes of carbon which are made up of entire carbon in the form of hollow spheres. Spherical fullerene is also known as buckyballs. It is used as a carrier for genes and for delivering drugs. The HIV replication can be suppressed by several antiviral compounds by using fullerene and its derivatives. The fullerene contains 12 pentagons and 20 hexagons, all the double bonds are conjugated and all the rings are fused. The antiviral activity of fullerene derivatives depends upon their unique molecular structure. Dendrofullerence 1 has the highest anti-protease activity, Trans-2 isomer, the second derivative has strong inhibition of HIV-1 replication. Fulleropyrrolidines with two

groups of ammonium are found to be active against HIV-1 and HIV-2[21]. The main two targets for anti-HIV fullerene derivatives are the HIV protease and the reverse transcriptase enzyme. The C20 which is the smallest fullerene can act as HIV RT inhibitors. The malonic acid and the aminoacid-type C60 derivatives have inhibitory action against the HIV RT [22].

MICROBISIDES

The topical microbisides have the clear potential for preventing the transmission of HIV, through sexual intercourse. It consists of products that can attack the viral or cellular targets and also prevents the infection of targeted cells or by inhibiting the replication of the virus. The development of topical microbisides depends upon the biology of HIV infection in the vagina or rectum. The first generation of microbisides includes highly sulfated molecules and detergent-based approaches for preventing the attachment of the virus or by inactivating the infectious virus[23.] The microbisides are grouped into 5 classes.The known activity is recognized only for 4 classes.

CLASSIFICATION OF MICROBICIDES:

a) Surfactants or membrane disruptors.
b) Vaginal milieu protectors
c) Viral entry inhibitors
d) Reverse transcriptase inhibitors[24].

QUANTUM DOTS AND RODS:

The complex physiological checkpoint of our body is the blood-brain barrier which shows the restriction of free diffusion of circulating molecules. The BBB checkpoint allows the essential nutrients to enter but not the harmful substances. It limits the penetration of CNS drugs for neurological disorders such as HIV-associated encephalopathy. The bio-conjugated quantum dots are the nano-vectors and the fluorescent probes being designed for delivering the anti-HIV drugs across BBB. The quantum dots are nanocrystals which is a semiconductor ranging from 2 to 10nm. They possess few optical properties. The surface of QD can be stuck with functional groups like primary amine, carboxylic acids which are used for the conjugation of QD with targeting ligands. Proteins, antibodies, and drug molecules are attached to the surface of QD for the targeted delivery of HIV-infection[25]. The next generation nanomaterial of QD is Graphene quantum dots which have the potential of drug delivery at specific target HIV inhibition. It is synthesized by the multiwalled carbon nanotubes which exhibit the anti-HIV activity through the inhibition of reverse transcriptase. The drugs like CHI499 and CDF199 belongs to the class of non-nucleoside reverse transcriptase inhibitors[26]. The quantum dots are fluorescence-based biological imaging applications. The HIV and the envelope proteins which are labeled with Q-dots that visualizes the dynamic interaction between viruses and targeted human cell. For capturing the HIV two HIV-specific proteins are used:

a) Anti-gp120 antibody which binds to the gp120 glycoproteins of HIV
b) Con A lectin, a specific to high-mannose residues exposed on gp12[27].

NANOCAPSULES:

The nanocapsules range from 10nm to 1000nm which can be a solid or a liquid core. The drug can be placed inside a cavity. It is surrounded by a polymer membrane. The nanocapsule has a great interest because of its protective coating which is pyrophoric and easily oxidized and delays the release of active ingredients[28]. The lipid nanocapsules act as a carrier for molecular adjuvant or surface-displayed antigens which promotes the T-helper cells response. Envelope gp140trimerwith terminal his-tags are attached to the surface of lipid nanocapsules for delivering the drugs against HIV-infection.

DISCUSSION

The most available preventing measures for treating HIV infection is by Anti-retroviral drugs. Through the anti-retroviral drugs patients can able to get appropriate medication. But, due to the issues of bioavailability and poor solubility in the cellular and anatomical reservoirs is affected. Major disadvantages of ARV medicines are distribution of drugs to the non-targeted area, rapid clearance, and presence of drug metabolizing enzyme. Due to the above consequences the drug delivery is discontinued. Though, the drugs show the resistance, the HIV begin to propagate the infection and circulates in the host body.Thus, a delivery system is needed for delivering the anti-HIV drug to the targeted sites for controlling the issue of bioavailability and solubility. The most possible way of spreading HIV is through sexual transmission as it is the major route of infection because it contains more immunological cells. Among the people who are infected with HIV/AIDS, 50% of women account for infection through sexual transmission. The microbisides are the emerging nano-technological method for preventing the entry or binding of HIV to the host cells in the rectum or vaginal mucosa. It works by the mechanism which is involved in the targeting of the virus or by inhibiting the binding of virus to the target cells.The

microbisides are capable of breaking the chain of transmission through sexual intercourse. These can chemical, physical or biological barriers at the surface of mucosa. As it is discussed above that there are 5 classifications of microbisides. The following are the method of prevention of each type of microbisides:
a) **Surfactants**: It is active against many pathogens and interrupts the membrane of pathogens non-specifically.
b) **Vaginal milieu protectors**: It maintains the PH of vaginal canal at acidic within 4.0 - 5.8 that inactivates HIV.
c) **Entry inhibitors**: Interacts with the proteins of HIV and prevents the binding of HIV to CD4 cells.
According to the proverb "prevention is better than cure", the idea of microbisides finds a trustable strategy against HIV which is preventing the infection at the basic level, it is safe, cost-effective, socially and ethically acceptable by all.

CONCLUSION

An important disadvantage of ARV drug therapy, is decreasing of drugs in the viral reservoirs like lymphatic systems, central nervous system and lungs. At the same time higher doses of drugs is needed for long period of time. Long period therapy exhibits the resistance in HIV virus that leads to the failure of ARV drug approach. There is a hope in the field of nanotechnology in the treatment of HIV that improves the effectiveness of anti-viral therapy. Due to the nanosize of the nanoparticle they can able to enter upon the blood-brain barrier, central nervous system and cures the HIV infection in the brain.The hydrophilic as well as hydrophobic drugs can be easily incorporated through various nanoparticles and the route of administration includes oral application or by inhalation. As the nanoparticles have high stability, high carrier capacity, it may bring success rate beyond the ARV drug therapy.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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