INTRODUCTION

Chikungunya virus (CHIKV) is an arthropod-borne virus that is transmitted to humans by the *Aedes* mosquitoes [1]. It is an alphavirus of the Togaviridae family [2]. This virus was first isolated in 1952 during an outbreak of febrile illness in Makonde, a province in southern Tanzania [2]. Since it was reported in 1952, this virus has resulted in millions of infections in different parts of the world such as Asia, the Indian Ocean islands, Africa, Europe, and America [4]. Chikungunya can cause an abrupt onset of joint pains, fever, and erythematous skin manifestations such as a morbilliform rash, scattered hyperpigmentation, especially on the face, and aphthous-like ulcers [5]. The term “chikungunya”, literally meaning “that which bends up”, originates from Bantu language of the Makonde ethnic group and points to the curved stature of the patient due to the incapacitating joint pain [6]. Acute symptoms of chikungunya typically disappear in one to two weeks, but polyarthralgia is recurrent in 30–40% of the patients and may continue to afflict the individual for years [7].

Over the past 50 years, a number of re-emergences of CHIKV have been documented, mainly in Asia and Africa, with intermissions of 2–20 years [8]. CHIKV emerged in Kenya in 2004 and spread eastward to the Comoro Islands by January 2005 [9]. In 2005–2006, the outbreak spread to other islands in the Indian Ocean, such as La Réunion, Mauritius and the Seychelles [10]. The virus infected about one-third of La Réunion’s population, resulting in more than 266,000 cases with over 200 associated deaths [11]. The epidemic also spread to India. By the end of 2006, it was approximated that more than 1.5 million cases have been reported in 7 countries, with about 1.25 million of the suspected cases originating in India alone [12] CHIKV was also identified in Europe, believed to have been transported by infected travellers from regions afflicted with chikungunya [13]. The first epidemic outbreak in the north-east of Italy was reported between July and September 2007, with more than 200 human infections [14]. This outbreak exhibited, for the first time, the potential of CHIKV to move to ecological niches it hasn’t been observed in before, such as Europe and regions of the Western Hemisphere [15]. In 2013, CHIKV was reported in the Caribbean, marking its first documented autochthonous appearance in the Americas, from where it...
continued to spread [16]. In Brazil, the first reported case of autochthonous CHIKV was in September 2014, in Ampap, followed by an outbreak in Feira de Santana [4]. Chikungunya continues to be reported across different parts of the world. In these outbreaks, it was seen women were usually affected more than men, and adults (over 30 years of age) were more susceptible than children [10]. Recently, In India, outbreak of chikungunya has been reported in Guntur, Andhra Pradesh in September-October 2013 [17]. In 2010, Delhi witnessed an outbreak of CHIKV, after which only sporadic cases were reported. However, in August 2016, another massive outbreak occurred in New Delhi and the National Capital Region, (NCR) [18]. Three genotypes of CHIKV have been identified till date: West African, Eastern/Central/South African (ECSA genotype), and Asian genotype. In 1962, CHIKV was seen in Wentworth, New South Wales in 1963, with the epidemic lasting for 2 years, and was of the Asian genotype [5]. In the following decades, only scattered cases at irregular intervals were reported [20]. The re-emergence of CHIKV in 2006 was of the ECSA genotype [21]. The Indian Ocean lineage (IOL) virus, which originated from the ECSA genotype, is responsible for the re-emergence of chikungunya that occurred in India and the Indian Ocean islands in 2005-2006 [22]. In December 2013, through the Caribbean, Asian genotype of CHIKV was introduced to the Americas. In the outbreak in Brazil in 2014, two genotypes were reported: Asian genotype was found in Amapa and ECSA genotype was seen in Feira de Santana City [23]. In humans, CHIKV is transmitted largely by Aedes aegypti, mosquitoes of the genus Aedes. Aedes albopictus was discovered to be the second-largest transmitter of CHIKV as observed in case of the IOL virus that circulated during the Indian Ocean islands outbreak. Due to a mutation associated with the substitution of an amino acid in the enveloped glycoprotein (E1–A226V) the virus adapts better to this vector, increasing its ability to spread the virus [24].

In spite of the large number of human infections caused by CHIKV annually, no vaccine or treatment against the virus is currently available. The infection remains unfamiliar to a significant fraction of the population as well as health professionals. Clinical management of the disease is complicated and often requires laboratory tests for its diagnosis and confirmation, which is not available on a large scale. Hence, there is a need to devise novel strategies to diagnosis CHIKV with ease and to combat this virus.

Current Treatment

Currently, no specific antiviral therapy is available for the treatment of chikungunya. Combating of the disease involves treatment of symptoms. In majority of the patients, the acute symptoms resolve within a week or two [1]. Treatment of CHIKV arthritis includes use of analgesics such as paracetamol, opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Arthritis can be treated with NSAIDs, but they possess risks such as haemorrhage and renal insufficiency associated with severe forms of Chikungunya. Also, care should be taken in areas where overlap of dengue virus and CHIKV occurs, as NSAIDs can cause thrombocytopenia and hemorrhagic symptoms like gastrointestinal bleeding in a patient co-infected with dengue [25]. Symptoms of chikungunya fever have been shown to be reduced, in the short-term, by systemic corticosteroids [26] but they can be associated with augmented risk and complications in the acute phase [25]. The use of chloroquine phosphate to treat CHIKV arthritis has demonstrated mixed results [27]. If the pain is a neuropathic component, it can be treated with antidepressants or antiepileptic drugs [28].

No specific antiviral drugs against CHIKV are available in the market. Several drugs have been tested against CHIKV, in-vitro, to give positive results. One such drug is Ribavirin, but limited information about its efficiency is available [29]. Other examples include arbidol, chloroquine, favipiravir, and furin inhibitors. However, most of these compounds have modest activity and their in-vivo efficacy has not yet been assessed [30]. Recently, a small molecule, Pep I, which has already been successfully used against HIV and HCV, was repurposed against CHIKV and showed high antiviral activity in-vitro. The molecule was found to bind to nsP2 protease of the virus and prevent its replication [31]. No vaccines against CHIKV are currently available. Options like viral-like particles, recombinant antigens, chimeric alphaviruses, electroporated DNA, and virus attenuated by large-scale codon re-encoding, are being looked into but no commercial vaccine exists as of now [29].

Nanotechnology-based Applications against CHIKV

Nanotechnology is the application of particles with dimension(s) that in the nanometer scale [32]. Nanoparticles (NPs) offer an array of advantages for use in antiviral therapy. The small size of NPs can allow drug delivery into anatomically inaccessible sites [33]. Their large surface area to volume ratios facilitates accommodation of large drug payloads [34]. As their surface charge can be modified, NPs can cross negatively charged cellular membranes [35]. NPs have been seen to exhibit biomimetic properties [36], which can give rise to intrinsic virucidal activity against a range of viruses, such as that observed in silver NPs against a broad range of viruses such as HIV, HBV, HSV, among others [37]. Encapsulation of drug in NPs [35], modifications with polymers such as PEG [34] or formation of stable structures with NPs [38], can decrease the amount of drug required by enhancing stability and bioavailability (Figure 2). NPs can also be engineered with moieties that would target certain cell or tissue types to increase specificity to the target [39].

Nanoeencapsulation of drugs offers multiple benefits such as improved efficacy and bioavailability and controlled release of the therapeutic agent [40]. For example, in a study, encapsulation of sildibinin, a potential anti-HCV agent, by leptosomes increased its absorption into the cell as well as pharmacological effect when compared to the free molecule alone [41]. PLGA NPs loaded with Nelfinavir, an anti-HIV drug, exhibited increased solubility and oral bioavailability as well as sustained release of the drug in in-vivo studies in rabbits [42]. Acyclovir, an HSV-drug, when loaded in chitosan nanoparticles, displayed antiviral activity higher than that seen in free acyclovir against HSV-1 and the HSV-2 strains and no cytotoxicity in-vitro [43].

Functionalization of NPs can make them excellent vehicles of drug delivery and greatly enhances their activity. NPs can be modified with a number of substances, including antibodies for targeted drug delivery or the drug itself for enhanced activity. Oselamivir-modified silver NPs have been demonstrated to greatly decrease H1N1 infection by inhibiting the activities of hemagglutinin (HA) and neuraminidase (NA), prevention of DNA fragmentation, chromatin condensation, and caspase-3 activity in vitro [44]. In an in vitro study against HIV, glucose-coated gold NPs were functionalized with NRTI drugs abacavir (ABC) and lamivudine (3TC) to give an ester bond that can be cleaved under acidic conditions to render the hydroxyl group for chain termination. Based on this scheme, more complex GNPs with carrying various antiviral inhibitors simultaneously can be designed [45]. Chitosan NPs modified with transferrin and bradykinin B2 antibodies have been developed for the targeted delivery of siRNA across the BBB, into astrocytes to inhibit H1V replication [46]. Selenium NPs have been shown to possess low toxicity and excellent antiviral activity. Functionalization of selenium NPs with Oselamivir against H1N1 influenza virus showed high antiviral properties as well as constraint on drug resistance [47]. Modification of selenium NPs with amantadine, another anti H1N1 influenza agent, also gave similar results [48].

NPs can be employed for the delivery of nucleic acids to inhibit the replication of the virus. An example of the use of nucleic acid would be STP909 (by Sirnaomics), a nano-based potential drug integrating siRNA for the treatment of HPV16 and HPV18 genotypes of HPV. In vitro studies demonstrated duplex formation with the mRNA from the E7 genes in HPV16 as well as HPV18, and in vivo studies in rabbits also showed the antiviral activity of these NPs due to knock-down of the E7 gene by them [49]. STP702 (from Sirnaomics) is another polymer-based drug system which incorporates siRNA targeting the conserved region of influenza for antiviral activity against a range of influenza viruses [50]. Anti-herpetic siRNA-loaded NPs also gave positive results in mice due to the knock-down of nectin [51]. An instance of the use of DNA would be titanium dioxide NPs functionalized with DNA fragments and...
produced by using a polylysine linker as effective inhibitors of influenza A virus, in-vitro. These nanocomposites targeted the non-coding 3’ region of influenza A virus and could enter the cells without transfection agents [52]. siRNA encapsulated in lipid NPs have been shown to target the Makona strain of Ebola virus in vivo in rhesus monkeys [53]. Dual-antibody-modified chitosan NPs when used to transport siRNA across the blood-brain barrier (BBB) target HIV-infected brain astrocytes and inhibit replication of the virus [46].

The novel technology of capture of the virus can be extended to the treatment of chikungunya. ‘Nanotrap’ particles are thermoresponsive hydrogels capable of capturing antigens by binding of bait to the particles by affinity. Live infectious virus, viral proteins and viral RNA can be captured by these Nanotrap particles [54]. Sialylneolacto-N-tetraose c (LSTc) bearing decy liposomes have been used to capture influenza A viruses, inhibiting the infection of cells in-vitro [55]. It has been demonstrated that graphene oxide (GO) nanomaterial can effectively capture viruses and destroy their surface proteins, consequently extracting their viral nucleic acid in an aqueous environment due to the superficial bioreduction of GO [56]. Modification of GO to give sulfonated magnetic NPs functionalized with reduced graphene oxide (SMRGO) was shown to capture and photothermally kill HSV-1. This system consisted of graphene sheets anchored uniformly with spherical magnetic NPs of different sizes [57].

NPs are also being developed as potential vaccines. Immense research is going into the development of NPs to provide immunity against viral infection. NPs offer a range of advantages over conventional vaccines. They can overcome disadvantages of traditional vaccines such as in vivo instability, weak immunogenicity, potential toxicity and the need for multiple administrations [58]. NPs can be used as carriers and for presentation of biomolecules on the NP [59]. Polymer NPs and liposomes, among others, can be used to encapsulate antigens. The antigen will be released on deconstruction of the nanoparticle inside the cell or in vivo [60]. When the NP is functionalized with the antigen, will be taken in by the cell along with the NP and released inside the cell [60]. In a study, chitosan NPs were used to encapsulate and deliver HA-split influenza virus product, producing greater immunogenicity than HA-split influenza virus alone in mouse models [61]. In another study, inactive swine flu influenza virus antigens encapsulated in PLGA NPs showed enhanced immune activity in pig models [62]. Gold nanorods modified with fusion protein (F), protective antigen of the Respiratory Syncytial Virus (RSV), produced positive results when tested in-vivo [63]. Double-layered protein NPs, produced by desolvation of tetrameric M2e, a highly conserved protein in human influenza A viruses, into protein NP cores followed by coating these cores by cross-linking headless HAs, have been shown to hold great potential as a universal influenza vaccine. These NPs resembled virion surface antigen display and size, making them highly immunogenic to generate immune protection against influenza A viruses [64].

Viruss-like particles (VLPs) are non-infectious, non-replicating nanoscale structures that assemble identical to native virion, consisting of viral proteins but no viral genetic material. Their ability to act as carriers for antigens, drugs and genetic material, potential to modify these VLPs and their immunogenicity makes them a prospective system for a number of applications [65]. An example of their use for drug delivery would be the design of pH-responsive virus-like NPs with increased tumour-targeting ligands for tumour-specific delivery of doxorubicin and polyacrylic acid in a controlled manner [66]. Studies are also being conducted to develop these particles into a potential vaccine. For instance, HIV-1 VLPs made up of a viral capsid protein with native Env trimers on the surface, which could induce immune responses against HIV hold immense promise as a vaccine [67]. VLPs built from the HBV tandem core platform that present conserved antigens of influenza that mostly remain unchanged with time confer immunity against influenza-related illnesses in mouse models [68].

CONCLUSION

Since no specific antiviral therapy or vaccine is currently available against chikungunya, nanotechnology can potentially be applied to combat CHIKV. The use of nanotechnology against a variety of other viruses has already been demonstrated in-vitro as well as in some in-vivo models. These techniques can potentially be extrapolated against CHIKV. Some of these techniques were outlined here. Although the use of nanotechnology against viruses such as HIV, Influenza viruses, HSV and Hepatitis viruses has been studied widely, the potential application of NPs against CHIKV is unexplored. NPs possess a multitude of advantages over other conventional methods of therapy and these advantages can be exploited to provide a prospective therapy or vaccine against Chikungunya. Chikungunya has spread across the world and new cases continue to be reported worldwide every year. Hence, there is an immediate need to devise a therapeutic approach against CHIKV.

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