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Transmission of infectious viruses in the natural setting at human-animal interface

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A B S T R A C T

Most viral pathogens causing epidemics and pandemics are zoonotic, emerging from wildlife reservoirs like SARS CoV2 causing the global Covid-19 pandemic, although animal origin of this virus remains a mystery. Cross-species transmission of pathogens from animals to humans is known as zoonosis. However, pathogens are also transmitted from humans to animals in regions where there is a close interaction between animals and humans by ‘reverse transmission’ (anthroponosis).

Molecular evidence for the transmission of two zoonotic RNA viruses at the human-monkey interface in Rajasthan forests is presented here: a) the apathogenic Simian Foamy Viruses (SFV), and b) Influenza A viruses (IAV)-like virus, etiologic agent for human flu infecting wild Indian rhesus monkeys inhabiting Rajasthan forests.

The data provide critical information on ecology and evolution of viruses of Public Health relevance. During replication, viral genomes mutate along the transmission route to adapt to the new hosts, generating new variants that are likely to have properties different from the founder viruses.

Wild Indian monkeys are under-sampled for monitoring infectious diseases mainly because of the difficulties with sample collection. Monkeys are perceived as religious icons by the Hindus in India. It is extremely difficult to obtain permission from the Forest and Wildlife Department government authorities to collect wild simian blood samples for surveillance of infectious diseases caused by viral pathogens.

Reducing animal-human contact and affordable vaccination are two relevant anti-viral strategies to counteract the spread of infectious zoonotic pathogens.

Genbank Accession numbers: Indian SFVmac: ADN94420, IAV like virus: MZ298601.

1. Introduction

Most viral pathogens causing epidemics and pandemics are zoonotic, emerging from wildlife reservoirs. Due to rapid deforestation and habitat loss, wild monkeys move near human dwellings in search of food as natural food like buds, leaves and insects present in the trees are no longer available to the simians. Investigations on zoonotic emerging diseases have significant relevance for Public Health research, but wildlife studies are difficult to perform and control. It is not possible to predict outcome of the infection. In this dynamic, on-going process of cross-species transmission, mutations in the viral genomes occur along the transmission route as the viruses keep replicating and evolving, giving rise to new variants. Pathogenic properties of the viral variants are usually different from the founder virus. Various factors are responsible for the ‘spillover’ of pathogens from wildlife like Old World and New World nonhuman primates to humans or the reverse transmission of pathogens from humans to monkeys at the human-monkey interface (van der Kuyl Antoinette, 2021; Olival et al., 2017).

Partial molecular sequences data of two new zoonotic viruses are presented here, a) Indian macaque Simian Foamy Virus (SFV) which are apathogenic in vivo, and b) H1N1 Influenza A viruses (IAV)-like virus infecting feral Indian rhesus monkeys from the Indian State of Rajasthan.

2. Simian foamy viruses (SFVs)

SFVs are complex retroviruses that infect nonhuman wild primates in Africa and Asia (Leendertz et al., 2008; Mouinga-Ondemé et al., 2010; Jones-Engel et al., 2005a). Humans in close contact with the primates get infected but the infection is not pathogenic. Foamy viruses infect different mammalian species, such as nonhuman primates (NHPs), felines, bovine and equine species (Ledesma-Feliciano et al., 2019).

Simian Foamy Viruses (SFVs) have been shown to naturally infect many nonhuman primates (NHPs), including Old World primates (OWP), New World Primates (NP), and prosimians. For over 60 years, most foamy virus research has focused on SFV infection in OWP (Fuentes et al., 2020; Switzer et al., 2004; Santos et al., 2019; Calattini et al., 2007; Wolfe et al., 2004; -Ondemé Augustin et al., 2011; Murray Shannon and Linial, 2019; Kehl et al., 2013; Rejane et al., 2014).

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Two-way transmission of viral pathogens from simian to human and vice versa.

Fig. 1. A population of wild rhesus monkeys (Macaca mulatta) from the natural habitats close to the cities of Jodhpur and Jaipur was included in the investigation. Cases of monkey bites as shown here, are routinely reported in the local press. Viral pathogens are transmitted not only from wild monkeys to humans, but also from humans to wild monkeys via ‘reverse transmission’.

Analyses of partial sequence data of genomes of two different viruses are included in the report, Simian Foamy Viruses (SFV) and human H1N1 Influenza A Virus, that were found to infect wild Indian rhesus monkeys. While SFV infection of different species of nonhuman primates is well documented, natural infection of wild Indian rhesus monkeys by SFV was not reported before. In vitro infection of normal PBMCs by Indian SFV caused typical syncytia formation, as shown here. Natural infection of wild rhesus monkeys by human H1N1-IAV-like virus from the natural habitat in Rajasthan is suggestive of human to simian ‘reverse transmission’ of pathogens. Sequence analyses of the hemagglutinin (HA) gene of ‘IAV like’ virus infecting wild rhesus monkeys revealed several point mutations and a deletion of 9 amino acid residues at the Carboxy terminal end of the translated amino acid sequence compared to the human IAVs. These changes are likely related to adaptation of the human virus in the simian host.

Naturally acquired SFV infections were described in a group of hunters living in Cameroon, central Africa. In Cameroon, 3.6% of people who were severely bitten and otherwise injured while hunting gorillas and chimpanzees had detectable SFV infection. In Asia, several simian species are infected by SFVs. People in frequent contact with various macaque species in Asia are also infected with foamy viruses (Jones-Engel et al., 2005b). In Bangladesh, infection with simian foamy virus (SFV) is ubiquitous among rhesus macaques, which come into contact with humans in diverse locations and contexts throughout the country (Feeroz Mostafa et al., 2013).

Spumaretroviruses are distinct from other retroviruses in their mode of replication. Ortho retroviruses such as Human Immunodeficiency Virus (HIV) are RNA viruses that reverse transcribe their genomes into complementary DNA (cDNA) which integrates as provirus into the chromosome of the target cell. In contrast, the reverse transcribed RNA genome of Spumaviruses in the DNA form is present during assembly and/or release, like the hepadviruses such as hepatitis B Virus. They bridge the gap between Orthoretrovirinae and Hepadnaviridae (Taylor and Winterton, 2017).

Simian Foamy viruses were first described in 1954, subsequently followed by isolation from a nasopharyngeal carcinoma of an African patient, by zoonotic transmission of a chimpanzee FV to a human. This virus was originally designated human foamy virus (HFV), currently called primate/prototypic PFV (Puentes et al., 2020). A true human variant has not emerged yet. FVs infect Old and New World Monkeys (OWM, NWM) and apes, where they induce little pathology. In cell culture studies, FV infection results in strong cytopathic effects in vitro, forming large syncytia in the target cells, resembling foams (Fig. 1). FVs establish lifelong latent infections without evident pathology in the host. The roles of cellular factors in FV replication are poorly understood. Foamy viruses encode the canonical gag, pol and env genes flanked by the long terminal repeats (LTRs) and additional accessory genes designated as tas (formerly designated as bel 1) and bel2 open reading frames (ORF). The accessory gene Bet is transcribed by a spliced product of the N-terminal tas and the complete bel2 ORF (Lindemann et al., 2021).

FVs probably had their origin as far back as 400 million years ago. An endogenous foamy-like element was found in the Coelacanth genome, an ancient living fossil from the Devonian period of the Paleozoic era (Ruboyianes and Worobey, 2016). Moreover, recent results indicate FV infection in the primate (aye-aye), a long-fingered lemur, native of Madagascar, and a Chinese bat (Wu et al., 2012).

A candidate for interspecies transmission is the newly discovered RaFV-1 bat virus. Bats are known to be a rich source of different pathogens that are subjected to various interspecies transmission events (Wang and Anderson, 2019; Role of Endogenous Viral, 1146). Compared to other retroviruses FVs show several distinct features that make them unique. FV's replicate only in the differentiating epithelial cells of the oral mucosa in vivo and are efficiently secreted into saliva in the natural hosts. SFV is highly prevalent and efficiently transmitted through saliva among rhesus macaques (Huang et al., 2012). Some human infections have been documented, but human-to-human transmission has not been reported.

Remarkable properties of FVs include the existence of an internal promoter (IP) site in the viral genome, partially reverse transcribed DNA as viral genome (like HBV), Gag-independent translation of Pol as well as particle assembly and virion egress due to the unique features of FV Gag
and Env proteins. The Integrase gene in the pol region of SFV genome is highly conserved, which is used in the phylogenetic analysis of novel Indian SFV in the present report (Schweizer and Neumann-Haefelin, 1995; Schulze et al., 2011; Hamann Martin and Dirk, 2016).

India is host to multiple species of OWMs. Among the most widely distributed species are rhesus monkeys (Macaca mulatta), langurs (Semnopithecus entellus) and bonnet monkeys (M. radiata), the latter species is distributed mainly in south India. Natural infection of wild rhesus monkeys by SFV was published by us earlier as an Abstract (Nandi Jayashree et al., 2011). We have also reported novel Type D Simian Retrovirus (betaretrovirus) SRV-6 infecting wild langurs and SRV-7 infecting wild rhesus monkeys. An HIV-1 like SIV infects wild rhesus monkeys (Nandi et al., 2019; Nandi Jayashree et al., 2006). These simian species are typical to India and its neighbouring countries like Nepal, Pakistan and Bangladesh.

In the present report, novel Indian SFVs infecting wild rhesus monkeys are shown to form a separate cluster in the phylogenetic tree, and are different from all African and Asian SFVs, including SFVmac (X83292) from the Genbank database confirmed that Indian SFV reported here constitute a separate and distinct cluster, related to published Asian SFVs but different from African SFVs.

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In the present report, novel Indian SFVs infecting wild rhesus monkeys are shown to form a separate cluster in the phylogenetic tree, and are different from all African and Asian SFVs, including the SFVmac sequence available in the Genbank database (X83292). We present sequencing data from the highly conserved Integrase gen (pol region) of SFV genome that infect wild rhesus monkeys from Rajasthan (Figs. 1 and 2).

3. Influenza a virus (IAV)

Wild Indian rhesus monkeys from Rajasthan forests are also infected by an IAV H1N1 like virus, (GB Accession Number: MZ298601) not reported before (Figs. 1 and 3).

Influenza viruses are enveloped, negative-sense RNA viruses of the family Orthomyxoviridae. Four of the seven genera (and species) of orthomyxoviruses are Alpha influenza virus (influenza A virus), Beta influenza virus (influenza B virus), Gamma influenza virus (influenza C virus), and Delta influenza virus (influenza D virus (Long et al., 2019)). Highly diverse Influenza viruses circulate in natural reservoir of wild, aquatic birds (Trinh et al., 2019; Poulsou and Brown, 2020).

IAVs cause pandemics when they are transmitted into human population via zoonosis and adapt to the human hosts by mutations in the RNA viral genome (Fukuyama and Kawaoka, 2011). Mutations in the zoonotic avian influenza virus (AIV) confer the ability to the mutated virus to bind to human cellular receptors and enter cells, replicate the viral RNA genome within the host cell nucleus, evade host restriction factors and innate immune responses, which can then lead to human-to-human transmission. The timing of pandemics cannot be precisely predicted as it depends on ecological and virological factors. Not all zoonotic transmissions of influenza virus result in an epidemic or pandemic (Venkatesh et al., 2018; Causey and Edwards, 2008). The host range of an influenza A virus is determined by species-specific interactions between virus and host cell factors. The H1N1pdm09 virus emerged in Mexico in 2009, and quickly spread throughout the world, causing an estimated 60.8 million illnesses and at least 12,469 deaths from 2009 to 2010 in the United States alone (Arellano-Llamas et al., 2017).

In response to the antigenic shift observed in 2009, previously characterized nonhuman primate (NHP) models used to evaluate H3N2 and seasonal H1N1 virulence were reassessed using the pH1N1 virus. These studies revealed species-specific differences in the host responses between rhesus and cynomolgus macaques. Cynomolgus macaques infected with strain influenza A/California/04/2009 (H1N1) (pH1N1 Cal04) virus exhibited moderately severe clinical signs by day 6 post infection, with a concurrent activation of the inflammatory response genes in the lung. In comparison, rhesus macaques infected with the same pH1N1 strain remained asymptomatic despite sustained viral shedding for 21 days post infection (Skinner et al., 2014). This subclinical response

Fig. 2. SFV sequence analyses: three wild Indian rhesus monkeys M1, M2 and M4 were infected with novel SFV based on the analysis of the highly conserved Integrase gene of the pol region of SFV genome. Alignment of translated amino acid sequences revealed the presence of the conserved His 2, Cys 2 motif. Equivalent sequences from different African and Asian SFVs including SFVmac (X83292) from the Genbank database confirmed that Indian SFV reported here constitute a separate and distinct cluster, related to published Asian SFVs but different from African SFVs.
characterized by the absence of clinical signs following experimental infection has thus far limited the use of the rhesus macaque challenge models to assess candidate vaccine efficacy (SmithG. et al., 2009; Josset et al., 2012).

Influenza virus hemagglutinin (HA) binds to sialic acid (SA) moieties that are the terminal sugars linked to the larger glycans of glycoproteins and glycolipids on the surface of vertebrate cells (Shaw et al., 2013). Differences in the structure of these ‘sialylated glycoconjugates’ between species can determine species-specific susceptibility to influenza virus infection. HA from human-adapted viruses bind α2-6-linked SA whereas AIV HA binds α2-3-linked SA.

Neuraminidase (NA) is a membrane-bound viral sialidase found on the surface of infected cells and virions. NA cleaves SA from the cell surface during the final stages of the replication cycle, enabling the release of progeny virions (Russier et al., 2016). The HA and NA genes are particularly variable in sequence, and at least eighteen HA and nine NA subtypes are perpetuated in the wild waterfowl natural reservoir (Byrd-Leotis et al., 2017; Yan et al., 2019; Nandy et al., 2014).

Bats represent a natural reservoir for several pathogens including Ebola virus, Hendra virus, rabies virus and SARS and MERS coronaviruses. The identification of new IAV-like viruses, HL17NL10 and HL18NL11, H17N10 and H18N11 has expanded the number of potentially zoonotic IAVs. However, the homologs of HA and NA of bat IAV are unable to interact with sialic acid residues despite a high degree of structural homology with their conventional counterparts. The HAs of bat IAVs make use of the major histocompatibility complex class II proteins of different vertebrate species to gain entry into host cells, potentially permitting a broader host tropism (Karakus et al., 2019).

Multiple molecular properties contribute to the in vivo phenotypes of IAVs, one of the most impactful properties that helps govern IAV host range is the receptor-binding activity and specificity of the HA protein. The enormous diversity and high rates of replication leading to virus evolution through mutation of viral genomes help them to adapt to humans in various parts of the world.

Swine IAV worldwide sustain many diverse H1N1, H1N2, and H3N2 virus lineages that frequently exchange segments via reassortment, producing a wide variety of progeny reassortant viruses. Pigs have been termed “mixing vessels” or intermediary host in which avian and human viruses undergo reassortment. Viral factors that play a key role in IAV virulence are the surface glycoproteins HA and NA, the polymerase complex, and the non-structural protein NS1. HA protein is a main determinant of organ tropism of IAVs.

The simultaneous outbreaks of influenza in humans and pigs during the 1918 pandemic raised questions if the virus had transmitted from pigs to humans, or humans to pigs (Nelson and Vincent, 2015). In the early time period, flu outbreaks appeared to represent a novel disease in pigs, whereas humans already had a long history of influenza pandemics, which suggested that human-to- swine reverse transmission was more likely. The 1957 Asian flu and 1968 Hong Kong flu pandemics involved influenza viruses of avian origins (Go et al., 2012). In these cases, the viruses were clearly human-avian virus “reassortants.”

Humans are periodically infected with avian viruses, and it is possible for reassortment to occur between an avian-origin virus and a seasonal human influenza virus during co-infection. IAVs experience strong competition in nature, limiting the range of reassortant progeny that are...
fit enough for onward transmission in nature. Although intra-subtype reassortment occurs frequently in humans, larger reassortment events between cocirculating H1N1 and H3N2 viruses do not produce viable progeny, except the lone example of a H1N2 virus that circulated from 2001 to 2003. Later reports demonstrated reassortants of swine and human IAVs (Donatelli et al., 2016; Deng et al., 2015).

4. Material and methods

Blood samples of wild Indian rhesus monkeys from the natural habitats were collected by temporary capture of the simians by veterinary professionals, with necessary permits from the Rajasthan Forest Department on several occasions starting in 1998 (35 rhesus monkeys: RM), 2003 (20 RM), 2007 (15 RM) up to 2010 (6 RM). Purification of PBMCs was conducted in a pathology laboratory at Jodhpur, Rajasthan. Blood samples were collected from wild rhesus monkeys in EDTA-K2 tubes under ketamine HCl anaesthesia (10 mg/kg body weight) in specially designed cages. Bananas and groundnuts were used as baits. Animals were released in the natural habitat after phlebotomy. Plasma and PBMCs obtained after Ficoll separation were kept frozen. Amplification of HA genes of IAV like virus infecting wild Indian rhesus monkey were based on sequences from published report (Deng et al., 2015). Amplificon sizes were as anticipated.

Table 1

| Primer name            | Primer sequence 5’-3’                |
|-----------------------|-------------------------------------|
| Outer Integrase Forward F1 | GCCACCAAGGGAGTATGCTG G           |
| Outer Integrase Reverse R1 | GCCACCAAGGGAGTATGCTG G           |
| Nested Integrase Forward F2 | CCTGATGAGAGTATGCTG G           |
| Nested Integrase Reverse R2 | GAAGCCGCTTATGCTG G           |
| Seasonal H1N1 HA fragment 1 | TGTAACACGGGCGTCAACCAATGGAAG  |
| Seasonal H1N1 HA fragment 1 M13 F | CAGGAACAGCTATGAGCGTAATGCTCCTTTCTCT |
| Seasonal HA II M13 F | TGGATAACAGGGACGTAATGCTCCTTTCTCT |
| Seasonal HA II M13 R | CAGGAACAGCTATGAGCGTAATGCTCCTTTCTCT |
| Pandemic pdmHA-I-M13F | TGGATAACAGGGACGTAATGCTCCTTTCTCT |
| Pandemic pdmHA-II M13 F | TGGATAACAGGGACGTAATGCTCCTTTCTCT |
| Pandemic pdmHA-II M13 R | TGGATAACAGGGACGTAATGCTCCTTTCTCT |

a) SFV Primers for amplification of the pol (Integrase) gene (Schulze et al., 2011).

b) AV primers for the amplification of HA genes of IAV like virus infecting wild Indian rhesus monkey were based on sequences from published report (Deng et al., 2015). Amplificon sizes were as anticipated.

5. Results

Majority of the animals (98%) gave positive signals for SFV Integrase genes (Fig. 2, rhesus monkeys M1, M2 and M4). One rhesus monkey (M3) gave positive signal for the HA sequences of IAV (Fig. 3). The hemagglutinin sequence of IAV H1N1-like virus infecting feral rhesus monkey M3 was highly homologous to equivalent sequence of the pandemic IAV sequence from Puerto Rico (1934) in multiple sequence alignment of the translated amino acid sequences. However, on pairwise comparison of amino acid residues of translated HA protein of IAV infecting wild Indian rhesus monkeys, M3 with H1N1 IAV Puerto Rico 1934 and other human IAVs revealed several point mutations and a deletion of 9 amino acid residue near the carboxy terminal domain (CTD) as shown in Figs. 1 and 3. The implication of the long deletion is not clear at this point but is likely related to adaptation of the human H1N1 IAV to infect the wild rhesus monkey host, M3.

Sequence data generated were first searched for homology using Blast and subsequently analysed by the corresponding author at Pune, India using genomic software programs, Clustal W, Clustal Omega, MEGA (Sievers and Higgins, 2018; Larkin et al., 2007; Tamura et al., 2013).

Clustal Omega and ClustalW are multiple sequence alignment program that products biologically meaningful multiple sequence alignments (MSA) of divergent sequences which are then used to generate respective phylogenetic trees. Evolutionary relationships can be seen via viewing Cladograms or Phylogenograms. Phylogenetic trees were constructed using Molecular Evolutionary Genetics Analysis (MEGA) according to the published report (Tamura et al., 2013). Multiple sequence alignment of the translated amino acid sequences revealed that Indian SFV macaques infecting wild rhesus monkeys is different from available SFV macaque sequences from Genbank X832925SFVmac. Indian SFVs from wild rhesus monkeys are unique and form a distinct cluster though appear to be related to available Asian SFV sequences and totally different from African SFV sequences in the phylogenetic tree (Fig. 2).

Natural infection of wild Indian rhesus monkeys by Influenza viruses, highly homologous to human Influenza A Virus (IAV) H1N1 sequences using primers from the HA region (Table, Fig. 3), following published report (Deng et al., 2015). The rhesus monkey (M3) H1N1 Inf A reveals a much higher homology with the human Puerto IAV 1934 and a related human IAV, (Accession number EF190982 Inf A virus), which is a viral reassortant between human and mouse IAV.

Infection of Wild Indian rhesus monkeys with human IAV H1N1 documented here represents an epidemiological phenomenon not previously reported (Fig. 3). Although we observed a broad similarity in the HA protein of Influenza virus from feral rhesus monkey M3 with
equivalent region of the Swine Influenza virus. In our analyses of the IAV H1A sequences, relatively lower similarity between M3 IAV and swine IAV suggest that swine IAV did not transmit the virus to rhesus monkeys (Fig. 3). On the other hand, the remarkable sequence homology of M3 IAV with human IAV suggests a human to simian reverse transmission or anthropomorphosis. (Zhang et al., 2018)

6. Discussion

We present novel data on two different human pathogens, Retroviruses and Orthomyxoviruses that impact both NHP and human hosts, based on sequence data from the conserved regions of the viral genomes, an accepted strategy for molecular identification of novel viruses. The small samples size despite several visits to the field site for samples collection is an inherent problem in all field-based investigation.

Viral emergence is a multi-step process involving virus transmission to humans and subsequent human-to-human spread. In this dynamic, ongoing process, mutations in the viral genomes occur along the transmission route that give rise to new variants of the pathogens whose pathogenic properties are likely to be different from the founder virus. Investigations on zoonotic emerging diseases have significant relevance for Public Health research, although wildlife studies are difficult to perform and control, and it is not easy to predict outcome of the infection. Long term follow-up studies are only possible using micro-chip tagging in the natural setting.

To reduce zoonotic transmission, strategies need to be developed to reduce contact with animal hosts, while human-to-human transmission can be reduced by case isolation and vaccination, where effective vaccines are available.

Declaration of competing interest

All authors have read and approved the report. The authors declare no conflict of interest.

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