Simian Foamy Virus; ZOONOSIS

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ABSTRACT

Foamy viruses are complex and ancient retroviruses belong to genus spumavirus of reteroviridae family prevalent to nonhuman primate species. Simian foamy virus is found to have a zoonotic significance. Humans acquire SFV by means of frequent occupational and non occupational exposures with infected animals and their body fluids. Humans have no clear clues of pathogenesis yet and no pronounced clinical signs have appeared so far. A persistent latent infection in humans is obvious which may remain unnoticed as there is no adverse clinical picture of SFV infection in naturally infected humans. As SFV has non zoonotic origin before, but several evolutionary phases in cross species result in its zoonotic outcomes. Since studies have declared the ability of retroviruses to emerge from non pathogenic into pathogenic form, so well precautions are decisive to deter zoonotic SFV.

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1. INTRODUCTION

The retroviridae family comprises of two subfamilies and eleven genera based on their phylogenetic analysis (Coffin et al. 2021). Among the subfamilies are Spumaretrovirinae and Orthoretrovirinae. Retroviruses are well recognized for causing a variety of exogenous and endogenous diseases in vertebrates (Maeda et al. 2008; Goff 2013) such as malignancies associated with lymphomas, sarcomas, leukemias and various other pathogenic tumors of mesodermal genesis. They are also involved in cancer development in mammary tissues, liver, kidneys, lungs, and immunodeficient diseases such as AIDS (Acquired Immunodeficiency Syndrome) and autoimmune diseases (Coffin et al. 2021). However, there are some retroviruses which approved to be non-pathogenic.

Foamy viruses (FV) are also known as Spuma or Syncytial viruses which belong to the genus Spumavirus of the Reteroviridae family (Pinto-Santini et al. 2017). They are complex forms of archaic viruses with the origin of non-human primates (NHP). They are ubiquitous in their spontaneous natural hosts which take in cats, horses, cows, bats, and other non-human primates (Meiering and Linial 2001). They are not endemic in humans but many cases of human infections by foamy viruses have been reported so far. These oldest known viruses have been revealed to be co-evolved with the non-human primate species (NHPS) at a minimum of 60 million years ago (Switzer et al. 2004; Pinto-Santini et al. 2017). These are classified as feline foamy virus (FFV), bovine foamy virus (BFV), equine foamy virus (EFV), chiropteran foamy virus (CFV), simian foamy virus (SFV) and prototype foamy virus (PFV) which are well described by (Pinto-Santini et al. 2017). It is thought that all others have rare or even no significance as zoonotic pathogens except simian foamy viruses. Simian foamy viruses (SFV) comprise a third complex group of retroviruses (Buseyne et al. 2018). Primarily simian foamy viruses (SFV) are the pathogens of non-human primates, but their genetic modifications with time have made it a zoonotic infectious agent.

SFV's genome contains 3 retroviral genes i.e. *gag*, *pol,* and *env*, and 2 regulatory *tas,* and *bet genes. Gag*, *pol,* and *env* mRNAs are transcribed by *viral promoters and enhancers* located on *5'LTR* followed by splicing of *pol,* and *env* mRNAs. *Basal transcription of tas and bet is initiated by the internal promoter (IP) followed by activation of the second promoter in long promoter* transactivator *Tas. Activation of 5'LTR occurs, by Tas protein assembly but Bet protein is highly expressed and still is poorly understood. High* mutations in retroviruses are reported, mainly associated with error-prone reverse transcriptase.

The first ever case of SFV in a human was reported in 1971 in a Kenyan patient which give rise to the question of where this virus came into human cells. In Later years many cases of SFV were reported in hunters, laboratory personnel, and women in different regions of the world where there had been a good interaction between human and non-human primate populations. Researchers have reported that SFV was transmitted to humans through the bites of apes, gorillas, and small monkeys (Achong et al. 1971). In occupational and non-occupational ways of exposure to these NHPs veterinarians, lab attendants, zoo keepers, hunters, and pet owners are at risk of interspecific transmission of SFV.

Why are they called foamy or syncytial viruses? It is because they can produce rapid cytopathic effects (CPE) in the host's body tissue, leading to immediate syncytium formation and cell death ultimately (Linial 1999). Although SFV is not very common in the human population, it can be a source of other serious diseases. SFV can persist in humans for more than 20 years which creates a long-term illness in man. This chapter depicts the complete overview of the simian foamy virus with its history, genetic structure, and its increasing importance with the zoonotic perspectives, along with diagnosis and care management to save humans from these infections.

2. BACKGROUND HISTORY

Foamy viruses (FV) belong to retroviruses and are the ancient type of viruses. Due to their complex structure and dissimilarities to other types of retroviruses, they are categorized as the subfamily of

retroviruses, the Spumaretrovirinae. Foamy viruses are pervasive in their natural hosts mainly including nonhuman primates, cats, and cows. Human pandemics caused by HIV-1 (retrovirus) and influenza a (orthomyxovirus) originated from zoonotic infections.

In 1971, the very first foamy virus in humans was isolated from a human cell culture from a Kenyan patient with Nasopharyngeal Carcinoma (Achong et al. 1971). Phylogeny showed that it has the origin from the East African chimpanzee subspecies (*Pan troglodytes schweinfurtii*) and is named prototype foamy virus. However, interspecific transmission from chimpanzees to humans remained unclear (Murray and Linial 2006). In the 1970/80s many researchers reported contrary results about SFV occurrence in the human population reflecting the significant percentage of nonspecific serological activity and lack of confirmatory tests (Meiering and Linial 2001; Gessain et al. 2013). In 1995, the first confirmed evidence of the presence of SFV in humans was reported based on specific antibody tests and molecular assays in 3 monkey governesses and laboratory technicians (Schweizer et al. 1995). Different other groups of researchers have reported similar findings in multiple workers occupationally related to nonhuman primates and zoos from the USA, Gabon, Canada, and China (Gessain et al. 2013). SFV infection was also reported in 50 persons (mostly hunters) in Cameroon who had direct contact with the blood or blood fluids of NHPs. The majority of them were bitten by apes (gorillas, chimpanzees, and small monkeys (*Cercopithecus nictitans)) during hunting practices.* Recently SFV infection in women was also reported in the Democratic Republic of Congo (Switzer et al. 2012). Simian foamy viruses (SFV) were considered to be transmitted from nonhuman primate (NHP) hosts to humans in comparison to other retroviruses (Switzer and Heneine 2011; Khan 2009). To confirm the mode of transmission different studies have been carried out in different areas of the world where human and nonhuman primates interaction was high. In North America, Europe, Africa, and Asia's densely populated areas, the human population is settled near the richest biodiversity reservoirs so nonhuman primates have become part of their daily life (Sandstrom et al. 2000; Switzer et al. 2004). In cities, nonoccupational means of exposure include the form of pets, parks, and animal marketing areas (thousands can be seen) which are likely to transfer inter-species diseases like simian foamy viral diseases (Jones-Engel et al. 2006; Southwick et al. 2005). In occupation situations veterinary clinics, research laboratories, and hunting areas appeared to be potential sites for the transfer of cross-species diseases. It is appealing to note that human and NHP interaction is very high in Asiatic regions as compared to other areas of the world. Human and macaque companionship dates back to 25000 years in Southern Asia (Engel et al. 2013). Human-macaque mutualism in the context of routine life due to common geographical area is putting humans in danger of viral interspecies transmission. However, In Africa, bush meat hunting is a potential risk factor for SFV transmission to humans (Betsem et al. 2011).

Different studies declared that in nonhuman primates SFV seropositive can reach 75-100% in adults and SFVs can be in high concentrations to be present in the saliva of diseased animals. The potential sources of zoonotic transmission of SFV are apes, New World monkeys, and Old World Monkeys. Humans appeared to be more susceptible to apes' SFV than old-world monkeys' SFV and New World monkeys' SFV. Humans are more susceptible to SFV strains coming from their genetically related nonhuman primates (Switzer and Heneine 2011).

In humans, more than 100 cases of zoonotic SFVs are reported however not being considered as natural hosts. In humans, persistent infection can be caused due to Zoonotic transmission of SFVs (Gessain et al. 2013).

3. GENOMIC STRUCTURE

SFV's genomic organization includes three retroviral gag, pol, and env genes arranged from the 5' end and two regulatory tas and bet genes (Fig. 1). Viral promoters and enhancers are located on 5'LTR (long

terminal repeat) that transcribe gag, pol, and *env* mRNAs followed by splicing of *pol and* env *mRNAs.* Basal transcription of tas and bet is initiated by the internal promoter (IP) chased by activation of the second promoter in long promoter *transactivator* Tas that is needed for transcription from 5'LTR. Tas is also helpful in the regulation of transcription from IP. Activation of 5'LTR occurs when Tas proteins assemble (*Meiering et al. 2001)*. The other protein Bet is highly expressed and non-*structural but still is poorly understood (*Russell et al. 2005; Delebecque et al. 2006; Gärtner et al. 2009; Jaguva Vasudevan et al. 2013). Assays of western blotting showed that antibiotics are produced in Naturally-infected NHP that gives a strong reaction to Gag and Bet proteins. In FV in vitro detection, anti-Gag and anti-Bet antibodies proved to be useful (Pinto-Santini et al. 2017).

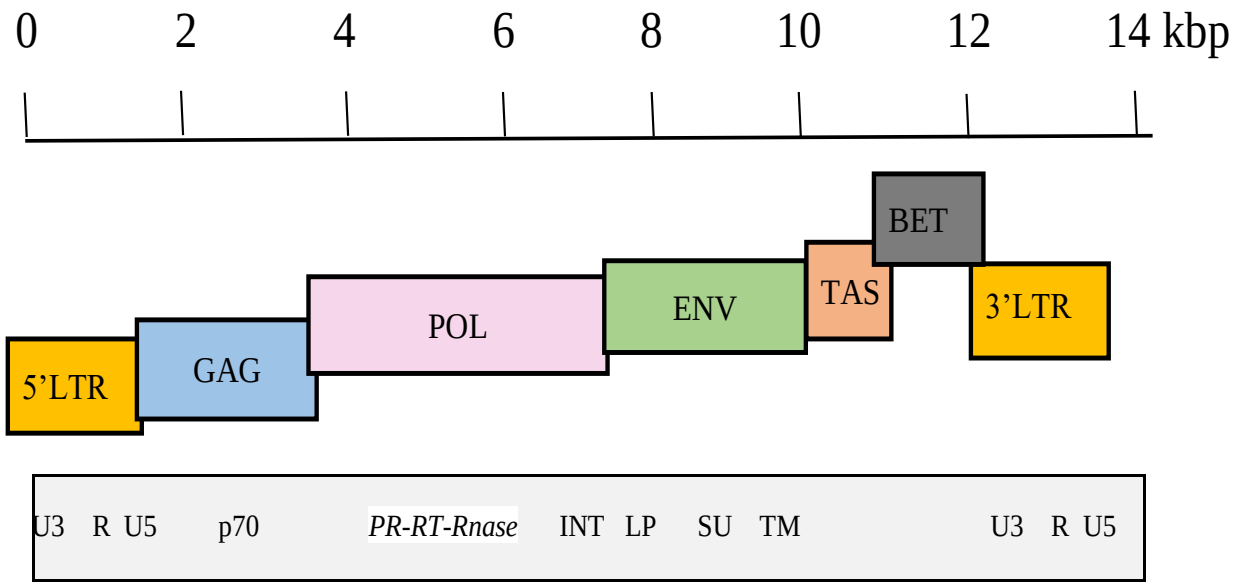

Fig. 1: Pictorial description of SFV genome (Chimpanzee strain). SFV genome is characterized by two flanking long terminal repeats (*LTR*) *that* contain 3 regions (a unique 3′ (U3), repeated (R), and *unique 5*′ (U5)). gag codes for both the shorter p70 protein and the full-length (74 kDa) gag protein. The protease (PR)-reverse transcriptase (RT)-Rnase H protein and the integrase (INT) are encoded by pol. The leader peptide (LP), surface glycoprotein (SU), and transmembrane protein (TM) are all encoded by env. tas and bet collectively code for regulatory proteins. Transactivator Tas binds to the 5'LTR and initiates the transcription of the structural genes gag, pol, and env.

Gag protein showed more similarity at the amino (N) terminus to other retroviruses as compared to the carboxylic (C) terminus (Linial et al. 2005). Just one cleavage near C terminus is reported resulting in ca. 3 kDa peptide, P3. A virus becomes non-infectious if a point mutation removes the Gag cleavage site resulting in a Gag full-length protein (Enssle et al. 1997). Cleavage is possibly needed for the configuration of leaved Gag protein and its function, however, it is not been proven yet. Maybe the P3 peptide has a significant role in replication. As almost half of formed Gag proteins are cleared, this leads to the existence of Gag doublet in Western blots (Pinto-Santini et al. 2017).

A high mutation rate in retroviruses has been reported. However, an interesting fact about foamy viruses is that their genome is highly conserved in personnel of the same kind of species in comparison to other retroviruses (Schweizer et al. 1999). Mutations in retroviruses are mainly associated with error-prone reverse transcriptase (RT). In vitro and cell culture examination of PFV RT has resulted in the similarity of PFV RT and recombinant HIV-1 RT in vitro (Boyer et al. 2007; Gärtner et al. 2009). However, a higher fealty RT probably has a supporting role in observed genome stability in FV. PFV recombination

is reported as a frequent event by template switching is significant as an error-prone RT, recombination may have a contribution to virus evolution. Recombinant viruses have been identified in SFV-infected OWM through sequence analyses of *gag* and *env* genes is strong evidence to prove the point of recombination in natural infection (Feeroz et al. 2013; Richard et al. 2015). The process of recombination, template switching, and recombination coupled with the documented interspecies transmission of FV in NHP give rise to the consideration of viral recombination of FV in co-infected animals of host species (Ghersi et al. 2015) (Fig. 2). In NHPs, co-infection with multiple SFV species has been reported. However, no case of coinfection and infection from recombinant SFV has been reported in humans to date (Leendertz et al. 2008; Liu et al. 2008).

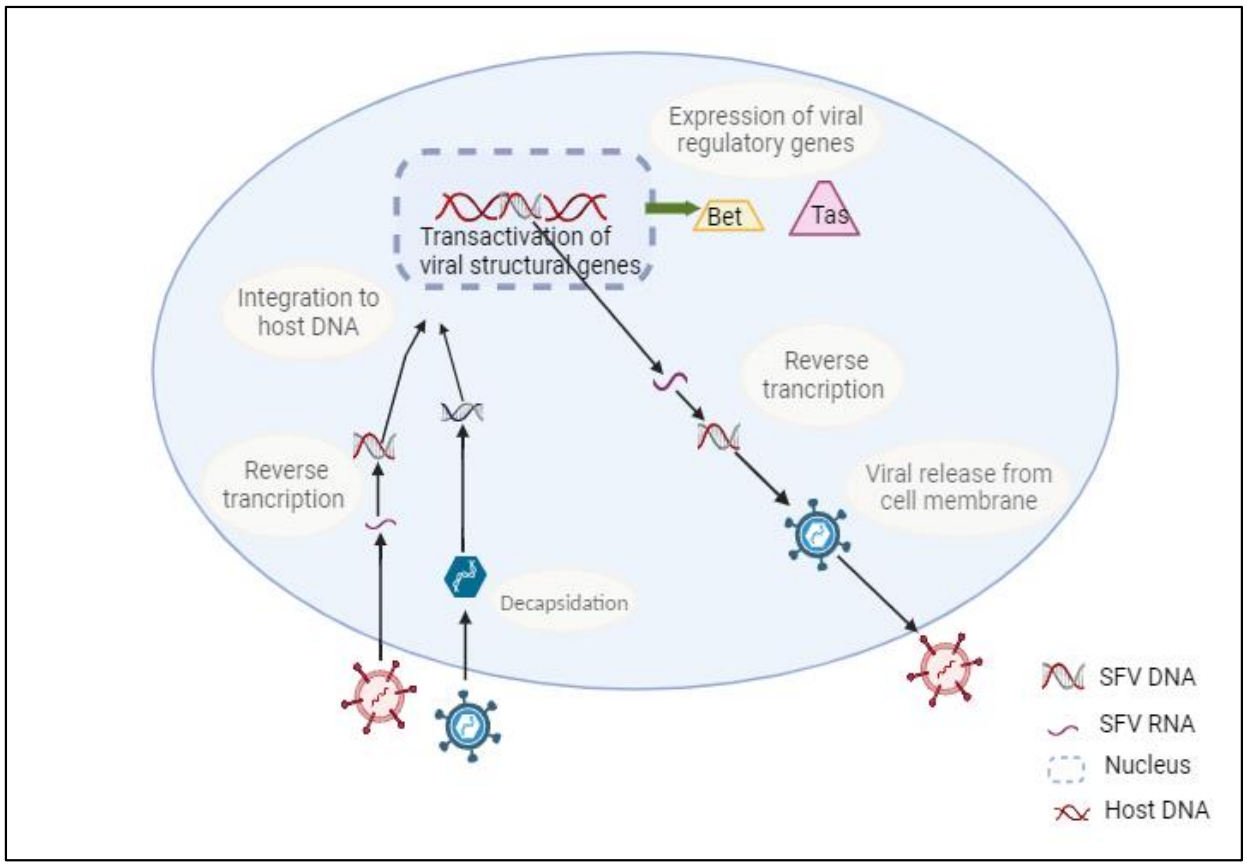

Fig. 2: Life cycle of SFV infection is stared with the decapsidation of RNA/DNA genome. In RNA containing SFVs reverse transcription occur followed by incorporation of DNA into host cell. *tas* and *bet* transcription induced by cellular activation of internal promoter followed by the activation of second promoter positioned on LTR by transactivator Tas resulted in the synthesis of Gag, Pol and Env proteins. After assembling and reverse transcription produce both DNA and RNA particles.

4. HOST SPECTRUM

Foamy viruses (family reteroviridae with the genus of spumavirus) can cause disease in a pervasive range of mammalian species, primarily non-human primates 10. Simian foamy virus has a zoonotic potential that leads to causes human infections. In them, the most obvious susceptible hosts are primates which includes monkeys and apes. The prevalence of this virus is more than 70% in monkeys

and apes 15. Simian foamy virus is more prevalent in their natural hosts than in humans. It infects a broad range of animal species mainly the non-human primates, monkeys, wild red colobus, and chimpanzees (Murphy and Switzer 2008). Moreover, SFV persists and causes asymptomatic infections in cats, sea lions, horses, hamsters, and cows (Wormser 2004). Among the non-human primates which harbor complex multiple strains of SFV are prosimians, baboons, African green monkeys, apes, macaques, and chimpanzees (Wormser 2004). Over time, the cross-species evolutionary modifications of the virus result in the infection in humans through various interactions with wild animals and non-human primate's species. But still, humans are rarely infected by this virus as its prevalence is not in domesticated animals. But still, as far as the genetic basis are concerned, it is well known that humans and monkeys are closely related species through their similarities in genetic makeup. The documented research claims that humans living or working in areas near the natural habitats of non-human primates are more likely to get viral entry into the body (Jones-Engel et al. 2008). However, evidence of natural infections in humans through foamy viruses is still lacking.

5. TRANSMISSION

Almost 60% of human infections are of animal origin which infects humans through numerous exposures either direct or indirect. In animals, the cross species Exogenous retroviruses have various routes of transmission from infected to healthy individuals, the most likely are through direct contact, bites, infected saliva, milk, blood, sexual contact, and perinatal routes (Pinto-Santini et al. 2017; Coffin et al. 2021). While the endogenous routes of viral transmission is vertical via the inheritance of germ-line proviruses (Coffin et al. 2021). The exact mechanism of transmission for foamy viruses is still needs to be known (Dhama et al. 2014). However, various research data suggest that the zoonotic simian foamy viruses are prevailing agents in non-human primates species. They are transmitted to humans through frequent occupational and non-occupational contacts with the infected animals, their body fluids, tissues, blood, or saliva (Khan 2009). The primary cause of viral entry to the human body is bite from NHP animals. These human bites are increasing with a great interest in hunting activities and increasing the load of the population of all NHP species in various geographical regions. In the significant blood-borne transmission SFV disseminates in humans during whole blood transfer, from SFV-infected humans. In this way, simian foamy virus is becoming a major health threat to human society.

6. PATHOGENESIS

The simian foamy virus is an endemic, zoonotic, and less prevalent retrovirus. Studies verified that only 2 to 3 % of humans get infected by SFV who are caretakers of non-human primates or lab workers dealing with the virus directly (Switzer et al. 2004). The exact pathogenesis characteristics related to SFV in humans are still unknown due to very minute data available. Worldwide, there are few humans affected by SFV which is mentioned in the literature. In this regard, the available analysis of a few subsets has not revealed the true picture of medical conditions associated with SFV (Hahn et al. 2000; Switzer et al. 2004; Brooks et al. 2007). Despite the very little information, some of the research data tried to elaborate on the pathological conditions caused by SFV in humans. It suggested that humans get the virus in through the NHP bites (gorillas, green monkeys, apes, chimpanzees etc.). The incubation period of SFV is highly variable from person to person. It may vary from 6 months to up to 3 years or more even. However, the virus's potential to cause significant infections in humans is lacking so far and needs to be understood deeply. Apparently, infected humans lack specific health problems (but it's according to limited personal

data), but deep *in-vitro* studies confirm a massive destruction of body cells caused by SFV in both monkeys and humans as well. The bites of non-human primates end with scars and significant wounds on different exposed parts of the body. Viral load is preferably seen in peripheral blood circulation and thus disseminated to the whole body. The virus specifically resides in the epithelial cells of the oral mucosa (Murray and Linial 2006; Falcone et al. 1999; Murray et al. 2008). SFV effects the liver, mucosa cells, and respiratory pars of the body during the course of infection (more commonly observed in non-human primates) (Ghersi et al. 2015; Muniz et al. 2017). Overall it is confirmed that SFV infection in humans is not as active as in non-human primates (Schweizer et al. 1997). The appropriate information for SFV pathological effects in humans is still unclear and further experiments are needed to confirm the exact path of pathogenesis in the human body.

7. VIRUS DETECTION

As the Simian foamy virus is an uncommon and limited studied virus, the specific detection methods or tests are not designed so far. To find the route cause of disease, we need subsets for analytical parameters. There are several biological and biochemical test methods for the diagnosis of viruses. The most reliable diagnostic techniques are serological and molecular testing. The simian foamy virus has a potential to cause a long-term non-significant infection in the human population as well. The samples from buccal mucosal epithelial cells, liver tissues, and blood especially from the peripheral body parts are obtained. The most preferred specimen is oral swabs where a huge number of the simian foamy virus are present. Most of the viral diagnostic practices are obtained from non-human primates which are the natural target animals for SFV. (Santos et al. 2019) elaborately described an experimental effort that in 2013, a large study has conducted on different genera of non-human primates to detect 192-bp *pol* sequence of SFV by using molecular technique i.e. PCR (polymerase chain reaction). In this experiment, the sample was collected from the peripheral blood mononuclear cells (PBMC) from wild monkeys and other NHPs (Ghersi et al. 2015). The conducted PCR assay results showed 100% sensitivity of the PBMC specimen from the western blot. Most of the samples were declared western blot positive which showed both sensitivity and specificity in wild non-human primate species (Santos et al. 2019).
Another detective method is serological testing in which specific antibodies are screened against simian foamy virus in the body. These antibodies include IgG and IgM which are specific immunoglobulin proteins. The research evidence by Hussain et al. (2003) showed a high level of seroprevalence among Asian and African NHP species, but it do not imply on humans until extensive deep research has to be done on the human population.

8. PREVENTION AND CONTROL

Zoonoses is a substantial public health problem which arises through a number of diseases which are common in different species of living things. It is a direct health hazard to human population leading to death. Among all of the human infections, almost 61% are of zoonotic importance in nature (Taylor et al. 2001). The interactions among humans, animals and the environment impose a significant role in the emergence and re-emergence, evolution and transmission of pathogens. With time, pathogens become genetically more stable and cause massive damage to the health and economy of the world. According to a survey study, there are about 2.4 billion estimated cases of zoonotic illness with the average of 2.7 million deaths of humans per year (Grace et al. 2012). In this way, there are certain prerequisites which are compulsive to adapt to minimize the adverse effects of pathogenic ailments over the globe.

Commonly, most of the zoonotic infections are transmittable from animals to humans by different means. Simian foamy virus is an emerging potentially zoonotic virus which is directly originating from wild animals. Humans need a comprehensive information of the SFV to carry out necessary measures to restrict the pathogen's survival and genetic stability.

9. INNATE IMMUNE CONTROL

In vitro investigations declared that Interferons are the molecules which are potent fighting force against viral diseases. Usually, they represent as the first line defence to the invading pathogens. SFV's can be easily sensed by the hematopoietic cells of human's defense system (Rua et al. 2012). It induces the production of higher levels of interferon-1 in blood. Interferon-1 (IFN-1) contains endosomal toll-like receptors which make it able to detect SFVs genome following the SFV uptake into the body (Rua et al. 2012). Moreover, these antiviral factors of interferon-1 hinders the virus replication inside the human body (Rua and Gessain 2015).

10. ADAPTIVE IMMUNE CONTROL

Foremost, the serum of infected individuals (experimented in rhesus macaques) have neutralizing antibodies which play crucial role to inhibit the SFV transmission and its infection (Williams and Khan 2010). Thus it aids *in vivo* adaptive control of SFV infections. There is no significant data showing the consequential events of immune system in humans after the SFV infection. However, antibodies have been found in SFV infected human's blood, saliva and urine samples which clearly depicts the adaptive immune control in human population against SFV (Rua and Gessain 2015).
Secondly, the neutralization event of Interferon-gamma with the activated PBMCs (Peripheral Blood Mononuclear Cells) in infected individuals leads to increase the viral expression (Falcone et al. 1999). It up-regulates the MHC-1 (Major Histocompatibility Complex-1) against SFV invading and replication inside the body (Colas et al. 1995). MHC-1 express the pathogen more efficiently and alert the immune system to virus infected cells of the body.

11. OTHER SALIENT CONSIDERATIONS

- SFV infected individuals are advised to not to donate blood to other individuals
- Use of PPE. As it spread more among humans who are occupationally linked to wild animals, veterinarians, butchers, hunters etc. They should adapt necessary measures while handling with the infected wild animal species such as washing of hands, use of gloves, properly covered body, cleaned hunting or other medical equipments, and proper repeatedly blood testing.
- Any cuts on skin should not be contaminated with infected animal's body fluids
- Minimize the usual contacts with wild animals (especially NHPs)
- Do not domesticate the non-human primates species
- Public awareness for zoonotic perspectives of SFV
- Adequate cooperation at regional, national and international level
- Proper wildlife monitoring committee
- Conservation of environment
- Adapt one health concept
- Availability of quick diagnostic facilities
- Ensure a safe food chain, especially for meat consumption

- Lunching of various educational programs related to zoonosis and hygiene

12. CONCLUSION

The greater part of human infections come from animal origin. SFV is at emerging state of infectious disease in humans. It has emerged through various evolutionary phases which enable its genomic stability. So far, it is an open gate to investigate various parameters of SFV emergence and control. However, the future of the SFV is completely unknown in the human population. There has not been any specific pathogenesis and apparent clinical picture in humans so far. That's why most of the basic parameters are yet to be investigated to conclude the outcome of zoonotic SFV infections. Some prerequisites and post-infection considerations are necessary to opt to deter the adverse effects of SFV.

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