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Origin, evolution and innate immune control of simian foamy viruses in humans

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Most viral pathogens that have emerged in humans have originated from various animal species. Emergence is a multistep process involving an initial spill-over of the infectious agent into single individuals and its subsequent dissemination into the human population. Similar to simian immunodeficiency viruses and simian T lymphotropic viruses, simian foamy viruses (SFV) are retroviruses that are widespread among non-human primates and can be transmitted to humans, giving rise to a persistent infection, which seems to be controlled in the case of SFV. In this review, we present current data on the discovery, cross-species transmission, and molecular evolution of SFV in human populations initially infected and thus at risk for zoonotic emergence.

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Most viral pathogens that have emerged in humans during the last century are thought to have originated from various animal species and are thus of zoonotic origin [1]. While the modes of viral dissemination within the human population are generally well characterized, the initial steps at the interspecies interface that lead to viral emergence remain poorly understood. Epidemiological field studies conducted in certain specific high-risk populations are thus crucial to obtain new insights into these early events of the emergence process.

Human infections by simian viruses represent an increasing public health concern. Indeed, non-human primates (NHPs) are considered to be the likely sources of viruses that infect humans and thus may pose a significant threat to human population [2]. This is well illustrated by some retroviruses, which have the ability to cross-species, possibly adapt to a new host and sometimes spread within this new species. It is now clear that the emergence of human immunodeficiency virus type 1 (HIV-1) and HIV-2 in humans has resulted from several independent interspecies transmissions. Different SIV types from chimpanzees and gorillas in the western part of Central Africa as well as sooty mangabeys in West Africa, gave rise to HIV-1 and HIV-2 respectively, probably during the first part of the last century [2]. Similarly, the origin of most Human T cell Lymphotropic virus type 1 (HTLV-1) subtypes appears to be linked to interspecies transmission between STLV-1-infected monkeys and humans, followed by variable periods of evolution in the human host [2]. In this brief review, we will present the current available data on the discovery, cross-species transmission and molecular evolution of the simian foamy viruses (SFV) present in different human populations at risk for zoonotic emergence.

Simian foamy viruses in humans

Since the initial description of foamy virus (FV) in rhesus monkey kidney cells in 1954 [3], such viruses have been isolated from several animal species, including numerous NHP species. The prevalence of FVs in naturally infected animals is generally high, but varies widely according to species [2]. Among NHP populations, SFV seroprevalence can reach up to 75–100% in adults [2]. In African green monkey and macaques, oral mucosa tissue is an important site for viral replication, explaining why foamy viral RNA is found at a high concentration in the saliva of such primates [4••]. Saliva-based means of transmission, such as bites, have been thus strongly suggested. Infection by SFV itself does not seem to cause any disease in infected NHPs, but studies have not been conducted to address this question specifically. However, when considering co-infections in macaques, SFV can increase the pathogenicity of simian immunodeficiency virus [5].

In 1971, the first human foamy virus was isolated from the cell culture of a Kenyan patient suffering of nasopharyngeal carcinoma [6]. Phylogenetic studies demonstrated that this virus originated from the East African chimpanzee subspecies (*Pan troglodytes schweinfurtii*). This strain is now considered to be the 'prototype foamy virus' (PFV). However, its exact origin remains unclear (*in vivo* cross-species transmission from a chimpanzee to the African

patient, or cell culture contamination) [7]. In the 1970/80s, several papers showed conflicting results on the presence of SFV in human populations and in different patients [8,9]. These findings reflected the high percentage of non-specific serological reactivity and the lack of specific confirmatory tests at that time.

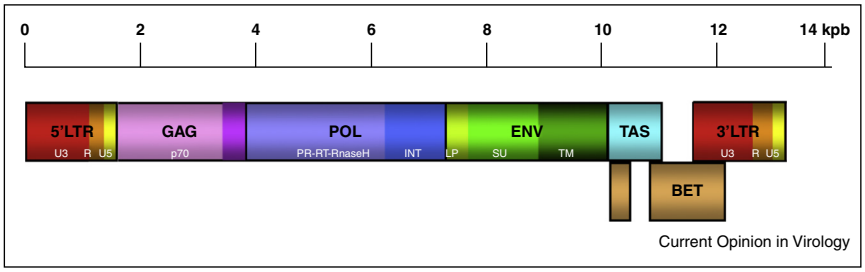
In 1995, based on specific serological and molecular assays, the first clear evidence of SFV in Humans was reported among 3 laboratory and monkey house personnel [10••]. Since then, other groups have reported similar findings in a series of workers occupationally exposed to NHPs in the USA and Canada and more recently in personnel from zoos or primate centers in Gabon and China [8]. Infection by SFV in a more natural setting was then demonstrated in villagers from Cameroon [11]. They were mostly hunters who reported direct contacts with blood and/or body fluids from wild NHPs. We extended such studies into different areas and populations of this Central African country and found the presence of SFV infection in at least 50 persons [12••]. The great majority of them (Bantus or Pygmies) were men who had been bitten by an ape (mostly gorillas but also chimpanzees) or a small monkey (mostly *Cercopithecus nictitans*) during hunting activities. A recent report from Gabon confirmed such frequent cross-species transmission in hunters after severe bites from mostly gorilla [13]. Infected women were also recently found in the Democratic Republic of Congo [14]. In South and Southeast Asian countries, SFV zoonotic infection has also been detected in various contexts of interspecies contact including 'monkey temple' workers, pet owners and people living around free-ranging macaques in South and Southeast Asia [15]. It is interesting to note that the Human/NHP interface in Asia differs greatly from that in Africa [16]. Human and macaques sympatry in Southeast Asia dates back as far as 25,000 years. Human-macaque commensalism is frequent in many monkey temples of these regions each year putting a very large number of persons, including tourists, at risk for macaques bites [17]. Indeed, human subjects in some South Asian countries came into contact with rhesus macaques mostly in the context of their daily lives, sharing a geographical area that is the 'home range' of both primate populations [16]. Such frequent interactions can lead to possible viral interspecies transmission. The situation is very different in central Africa where bush-meat hunting (including Apes such as gorillas and chimpanzees) is the major risk factor associated with SFV interspecies transmission [12••]. Furthermore, in Central Africa, the number of contacts between humans (mostly hunters and their wives and butchers) and potentially infected NHPs has probably greatly increased during the last century. This is believed to be due to increased hunting activities, resulting from a combination of urban demand for bush-meat, greater access to NHP habitats provided in part by logging roads, easier accessibility to fire arms, an increase in populations living in forest areas, and the associated increase in local food needs [2].

While nowadays, Humans are not considered to be a natural host of SFV, more than 100 cases of SFV infection have been reported so far in individuals in close contact with NHPs [8]. Among them, no specific pathology has been yet demonstrated. However, the selection bias inherent in the enrollment of healthy persons in the very few performed studies greatly limits the current ability to identify any potential associated disease.

SFV genomic organization and structural proteins

The SFV genome comprises the retroviral *gag*, *pol* and *env* genes, and two regulatory genes *tas* and *bet*. An internal promoter allows basal transcription of *tas* and *bet* (Figure 1). The transactivator Tas then activates a second promoter located in the long-terminal repeat, which induces the synthesis of the Gag, Pol and Env structural proteins. SFVs can also go through a late reverse transcription step, before the release of SFV particles. Thus, SFV particles can contain SFV RNA and SFV DNA genomes (Figure 2A) [18].

Figure 1



Schematic representation of SFV genomic organization (chimpanzee strain). The SFV genome is flanked by two long terminal repeat (LTRs) which contain the unique 3′ (U3), repeated (R) and unique 5′ (U5) regions. *gag* encodes the full-length gag protein (74 kDa) and the shorter p70 protein. *pol* encodes the protease (PR)-reverse transcriptase (RT)-Rnase H protein and the integrase (INT). *env* encodes the leader peptide (LP), the surface glycoprotein (SU) and the transmembrane protein (TM). Two additional genes *tas* and *bet* encode proteins having regulatory functions. The transactivator Tas binds to the 5'LTR which activates the transcription of the structural genes *gag*, *pol* and *env*.