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Primate and Feline Lentiviruses in Current Intrinsic Immunity Research: The Cat is Back

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Abstract

Retroviral restriction factor research is explaining long-standing lentiviral mysteries. Asking why a particular retrovirus cannot complete a critical part of its life cycle in cells of a particular species has been the starting point for numerous discoveries, including heretofore elusive functions of HIV-1 accessory genes. The potential for therapeutic application is substantial. Analyzing the feline immunodeficiency virus (FIV) life cycle has been instrumental and the source of some surprising observations in this field. FIV is restricted in cells of various primates by several restriction factors including APOBEC3 proteins and, uniquely, TRIM proteins from both Old and New World monkeys. In contrast, the feline genome does not encode functional TRIM5alpha or TRIMCyp proteins and HIV-1 is primarily blocked in feline cells by APOBEC3 proteins. These can be overcome by inserting FIV *vif* or even SIVmac *vif* into HIV-1. The domestic cat and its lentivirus are positioned to offer strategic research opportunities as the field moves forward.

Keywords

restriction factor; HIV-1; FIV; Lentivirus; TRIM5alpha; TRIMCyp; APOBEC3; innate immunity

I. HIV-1 and FIV: Pieces of the Puzzle

Lentiviruses have certain characteristic properties, such as macrophage tropism, the related capacity to infect non-dividing cells, and slow (*lenti*) disease progression. Even so, among the various members of this retroviral genus, FIV and HIV-1 are strikingly alike on several additional levels (Elder et al., 2010). FIV is the only nonprimate lentivirus that causes AIDS, and it is one of only two causes of pandemic AIDS. It enters cells via a T cell co-stimulatory molecule (Shimojima et al., 2004) and CXCR4 (Poeschla and Looney, 1998; Willett et al., 1997a; Willett et al., 1997b), it has a Vif protein that is needed to produce fully infectious virions (Tomonaga et al., 1992), and much like the situation with primate lentiviruses, feline lentiviruses infect numerous free-ranging feline species without doing much harm (Pecon-Slatery et al., 2008b). As with HIV-1, a relatively recent jump to a new host species, *Felis*

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Conflict of Interest Statement

The author declares that there is no conflict of interest.

catus, led to high immune virulence and an AIDS pandemic. Main lentivirus groups and their approximate phylogenetic relationships are diagrammed in Fig. 1.

Lentiviral vectors derived from HIV-1 and FIV have been used intensively in translational gene therapy research for a decade and a half (Naldini et al., 1996; Poeschla et al., 1998). However, in the past five years we have received a burst of requests for FIV vectors from HIV-1-focused basic researchers. A main reason is burgeoning interest, for compelling scientific reasons, in how cells of different species are intrinsically hard-wired for retroviral defense against the retroviruses of other species. One strong area of interest is how individual humans, *Homo sapiens* as a species, and various other primates and non-primates defend at the single cell level against lentiviral invaders and how they have done so over extended periods of time in the past (Bieniasz, 2004; Huthoff and Towers, 2008; Malim, 2009). The accumulating record suggests cycles of species-virus combat (selection and counter-selection) on evolutionary time scales (Sawyer et al., 2004; Sawyer et al., 2005). In one such cycle, *Homo sapiens* now finds itself vulnerable to HIV-1, which has evolved multiple ways to evade human restriction factors.

In numerous laboratories in the last few years, analyses of FIV life cycle phases using single-cycle subgenomic vectors have provided insights into species-specific restriction factors and their evolution (Diaz-Griffero et al., 2007; Dietrich et al., 2010; Fletcher et al., 2010; Ikeda et al., 2008; Javanbakht et al., 2007; Larue et al., 2010; Lin and Emerman, 2006; McEwan et al., 2009; Münk et al., 2008; Münk et al., 2007; Neagu et al., 2009; Poss et al., 2006; Saenz et al., 2005; Schaller et al., 2007b; Stern et al., 2010; Virgen et al., 2008; Wilson et al., 2008; Ylinen et al., 2010; Zielonka et al., 2010). There are related basic molecular lentivirology problems, such as HIV-1 nuclear import, integration and assembly, for which FIV vectors were used to shed light and raise new questions, e.g., (Kemler et al., 2010; Krishnan et al., 2009; Lee et al., 2010; Lin et al., 2010; Llano et al., 2006; Luttge and Freed, 2009; Luttge et al., 2008). In addition, distinctive properties of FIV and the cat proteome are generating specific interest in the prospect that restriction factor-based therapeutics could be tested in the cat (Dietrich et al., 2010; Neagu et al., 2009).

In summary, that FIV is not HIV-1 – but is both similar and different in informative ways – makes it relevant and in some instances unique. Retrovirologists are examining nonprimate lentiviruses with renewed interest as they reach for insights across species and back into time. In a related development, lentiviruses as a genus just got a lot older: minimum age estimates in the range of 12–14 million years have been inferred for recently identified endogenous lentiviruses in rabbit, hare and lemur genomes (Fletcher et al., 2010; Gifford et al., 2008; Gilbert et al., 2009; Katzourakis et al., 2007; Keckesova et al., 2009).

II. Restriction Factors, Primate and Otherwise

The phenomenon of species-specific restriction is not new to retrovirologists, but for many years the only clear example was in mice (Lilly, 1967), where a heritable and genetically dominant cellular factor called *FvI* was identified. Like one class of factors now known to restrict lentiviruses (TRIM proteins), *FvI* functions in cultured cells, is saturable by co-infecting with excess particles of any restricted virus, and the viral determinants map to the capsid protein (DesGroseillers and Jolicoeur, 1983; Hartley et al., 1970; Pincus et al., 1975). It was subsequently recognized that cultured cells from other mammals, including primates, had similar activities against retroviruses (Besnier et al., 2002; Besnier et al., 2003; Cowan et al., 2002; Hatzioannou et al., 2003; Hofmann et al., 1999; Münk et al., 2002; Towers et al., 2000; Towers et al., 2002). However, the murine and non-murine post-entry restricting activities turned out to be mediated by wholly different proteins (Best et al., 1996; Schaller et al., 2007a; Stremlau et al., 2004; Ylinen et al., 2006).

APOBEC3G (Sheehy et al., 2002), TRIM5alpha (Stremlau et al., 2004), TRIMCyp (Sayah et al., 2004), and Tetherin (Neil et al., 2008) are of greatest current focus for lentivirologists, but others are likely to be discovered. For example, there is evidence that the lentivirus protein Vpx targets an unknown cellular factor or factors for degradation in cells in the monocyte-macrophage lineages (Berger et al., 2009; Goujon et al., 2008; Goujon et al., 2006; Goujon et al., 2007; Gramberg et al.; Kaushik et al., 2009; Manel et al., 2010; Planelles and Barker, 2010; Schule et al., 2009; Sharova et al., 2008). Restriction factors make good sense to viral immunologists. Critical components of mammalian antiviral immunity include adaptive humoral and cellular mechanisms as well as "innate" systems like interferons. The latter can be triggered through pattern recognition receptors such as membrane bound Toll-like receptors or cytoplasmic receptors like RIG-I. But mammalian cells "ought to" and do have a faster, front-line immunity, one that can patrol cell compartments that a viral invader must cross and detect and neutralize it immediately before the more time-consuming mechanisms can come into play or a second cell -- and from there perhaps an entire species -- is threatened. These cell-intrinsic rapid response systems also tie into the other components of innate immunity. For example, their levels can be boosted by interferons (Koning et al., 2009; Neil et al., 2007; Neil et al., 2008; Refsland et al., 2010).

Restriction factors also make sense to evolutionary biologists, since it is clear that the property that most defines these proteins and prompted their discovery, which is their precise, intricate species- and virus-specificity, reflects repeated past selection events when populations were culled by viral pathogens (Huthoff and Towers, 2008; Sawyer et al., 2004; Sawyer et al., 2005). The reciprocity is an important aspect and gives rise to the proviso that a protein of interest with apparent retrovirus-inhibiting properties cannot reliably be called a restriction factor unless there is evidence that the virus or viruses in question have evolved a countermove. For HIV-1, known countermoves include Vif, Vpr, Nef and a variant capsid surface. Such dodges can be proteins like these, or even kinetic mechanisms that minimize single stranded DNA exposure (Hu et al., 2010). Impressively, it is now believed that the accessory genes of the primate lentiviruses (*vif*, *vpr*, *vpx*, *nef*) are largely devoted to countering restriction factors [see (Malim and Emerman, 2008) for a review].

This area also intersects closely with a fascinating recent corpus of work, a veritable science fiction story in real life: the decipherment of the origins of HIV-1 (Gao et al., 1999). Considering the bewilderment that greeted the pandemic's emergence thirty years ago, it is satisfying that we now know in biogeographic terms precisely where the main form of HIV-1 (the M group) came from. That is, it came from a viral lineage (SVIcpzPtt) that persists today in chimpanzee troops between the Boumba and Sangha Rivers in what is now the southeastern corner of Cameroon (Keele et al., 2006; Van Heuverswyn et al., 2007). The emergent virus most likely made its way from there down the Congo River basin to Kinshasa, where the group M pandemic was spawned. It turns out that both HIV-1 and HIV-2 have each arisen several times in humans, probably after inadvertent percutaneous inoculation of the blood of chimpanzees and sooty mangabeys respectively, but only one adapted fully to *Homo sapiens* and took off to generate the HIV-1 pandemic (Gao et al., 1999; Hahn et al., 2000; Keele et al., 2006; Korber et al., 2000; Santiago et al., 2002; Sharp and Hahn, 2010). Beatrice Hahn keynoted the recent feline retrovirus meeting in Charleston¹ with a telling of this still developing story [see for example (Worobey et al., 2010)] as well as presenting new data -- since published -- in which similar field and molecular techniques were used to determine the species origin of the human falciparum malaria parasite (Liu et al., 2010). Unlike non-human primate lentiviruses, FIV infection is worldwide, and unlike the chimpanzee/human connection, the domestic cat's closest living

¹10th International Feline Retrovirus Research Symposium (IFRRS), Charleston, South Carolina, May, 2010. This biennial meeting will be held in Leipzig in 2012.

relative *Felis sylvestris* does not harbor a lentivirus, suggesting that *Felis catus* acquired FIV sometime after domestication approximately 10,000 years ago (Driscoll et al., 2007; Pecon-Slattery et al., 2008a; Pecon-Slattery et al., 2008b; Troyer et al., 2008).

III. Cats and Carnivora: Thinking about *In Vitro* and *In Vivo* Models of Lentiviral Restriction and Disease

Restriction factors are discussed in several papers in this volume. Hind Fadel and I review lentiviral restriction factors and the lacks thereof in domestic cat and other Carnivoran cells (Fadel and Poeschla, 2011). Feliformia genomes do not encode functional TRIM5alpha or TRIMCyp proteins (McEwan et al., 2009) and the main feline cell restriction to HIV-1 is mediated by feline APOBEC3 proteins (Münk et al., 2008; Münk et al., 2007; Stern et al., 2010). Moreover the restriction to HIV-1 can be countered by inserting FIV *vif* or (surprisingly) SIVmac *vif* into HIV-1, which allows it to replicate productively in HIV-1 receptor-complemented Crandell feline kidney cells (Stern et al., 2010).

Conversely, we discuss recent evidence that if HIV-1 entry receptors are provided, the cat genome can supply the other dependency factors needed for productive HIV-1 replication (Stern et al., 2010). This is a fundamental difference with the mouse genome (Bieniasz and Cullen, 2000).

Can restriction factor research be exploited therapeutically? Certainly, interfering with the viral counter-defenses with small molecule inhibitors that, for example, disrupt Vif-A3 protein interactions, has interesting promise (Nathans et al., 2008). In terms of using the factors directly, there is also potential, but many questions remain to be answered. Brian Willett and colleagues discuss in this volume an engineered "felinized" TRIMCyp protein (Dietrich et al., 2010) analogous to one recently developed from human protein components (Neagu et al., 2009). What would happen if one could insert this or another restriction factor transgene into the genome of the cat? Or, through feline or human gene therapy, express a restriction factor in FIV or HIV-1 viral target cells?

The idea that this could protect the individual is an intriguing concept, and as an experiment it would be exciting for numerous reasons, not the least of which is that the hypothesis is a genuinely falsifiable one. Retroviral restriction factors have not been tested at the systemic level by experimental introduction into the germline or the relevant tissue compartment of a disease-susceptible species. Do restriction factors mainly prevent rare species-level transmission events in concert with numerous other defenses? Would introducing a single restriction factor *in vivo* work? Under what circumstances would it be adequate to prevent the initial establishment of HIV-1/FIV infection? Would it protect against both low dose mucosal and parenteral challenges? Would it work for a lentivirus with its prolific mutability or would the virus rapidly escape? Would it prevent systemic spread in an otherwise fully disease-susceptible mammalian host? Would the approach work in an already infected individual, or would the virus overwhelm (saturate) it when antivirals were withdrawn? Observational data in the murine Fv1 system and in primates (Kirmaier et al., 2010; Lim et al., 2010) provide grounds for certain inferences in this direction but not for clear answers. For reasons discussed above, the FIV model has potential for answering some of these questions. It can also be speculated that research in this area might, eventually and in the right circumstances, yield ways to confer protection from viral pathogens to free-ranging feline species, virtually all 36 of which are now threatened with extinction (Cleaveland et al., 2007; Johnson et al., 2010; Meli et al., 2009).

²Progress towards feline transgenesis was discussed at the Charleston meeting as well (Wongsrikeao and colleagues, unpublished data).

In conclusion, FIV is of current interest to HIV-1 researchers for numerous reasons and the Carnivora as a whole are also intriguing us as we look at their genomic complements of restriction factor genes. Felines and feline lentiviruses are likely to continue to offer strategic opportunities as the field moves forward. The very successful meeting in Charleston (Roca A, Meeting summary paper, this volume) provided an important intensive update on current feline retrovirus research. I was delighted to go from there to the more HIV-1-focused Cold Spring Harbor Retroviruses Meeting³ and not miss a beat in hearing researchers discuss FIV.

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³2010 Cold Spring Harbor Retroviruses Meeting, Cold Spring Harbor, New York, May, 2010.

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Fig. 1. Overview of lentiviral phylogeny
Approximate phylogenetic relationships are illustrated.