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Emergence of intracellular genetic parasites from ancient retroviruses

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Background

Endogenous retroviruses are genetic parasites of mammalian genomes. They are « remnants » of ancestral infections by retroviruses that had integrated into the germ line of the host and were then transmitted vertically, in a Mendelian fashion. Studies of several endogenous retrovirus families have led to the identification of functional elements, able to replicate inside the host. Whereas some endogenous retroviruses behave as *bona fide* retroviruses, with a replicative cycle involving extracellular viral particles, some of them disclose a strictly intracellular amplification cycle with viral particles accumulating in the cytoplasm or in intracellular organelles.

Results

Throughout the study of two such ''intracellularized'' endogenous retroviruses, the murine MusD and IAP elements, we have deciphered the molecular events that have led to their emergence during evolution. We show that these elements derives from ancestral retroviruses by alteration of the plasma membrane targeting signal of the Gag protein, leading to the intracellular sequestration of the virus-like particles, followed by the decay of the *env* gene coding sequence. We demonstrate that replacement of the N-terminal Gag domain of MusD or IAP by that of infectious retroviruses restores the targeting of their viral particles to the plasma membrane and their release in the cell supernatant. These particles can further be pseudotyped with a functional Env protein and become infectious, thus reconstituting a *bona fide* functional retrovirus. Symmetrically, we were able to convert a ''classical'' endogenous retrovirus, named IAPE, into a functional ''intracellularized'' element by modifying its N-terminal Gag domain (Fig. 1A and 1B). This modified element gained the ability to efficiently amplify via a strictly intracellular cycle (Fig. 1C).

Conclusion

These results led us to propose a scenario that accounts for the generation, during evolution, of very successful intracellular genetic parasites from ancient retroviruses.

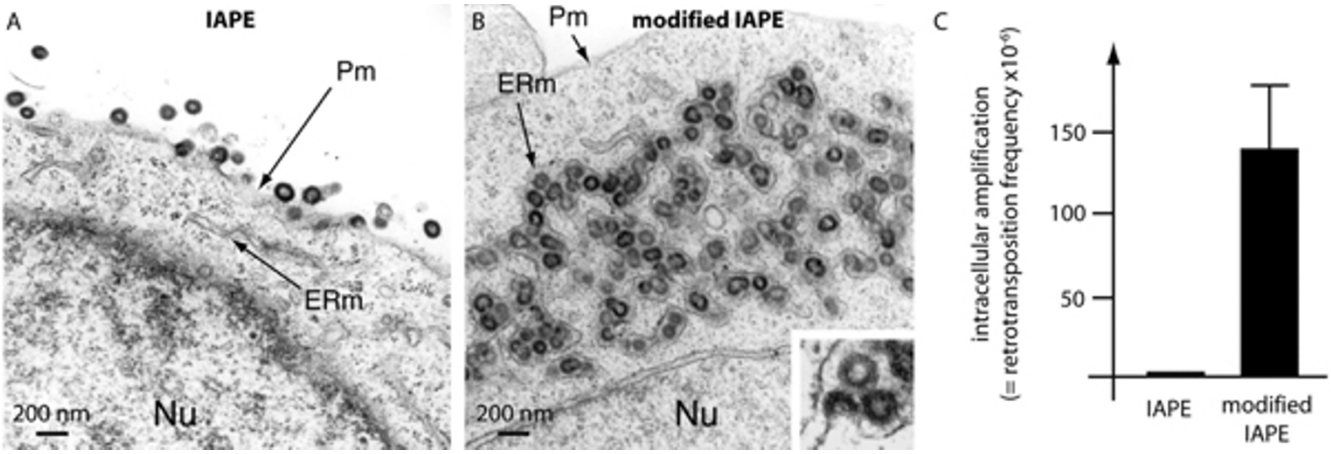

Figure 1

Conversion of a *bona fide* retrovirus to an "intracellularized" element. (A) Electronic microscopy images of viral particles produced by IAPE, a "classical" endogenous retrovirus, budding at the cell membrane. (B) Images of viral particles produced by a modified IAPE (in which the N-terminal domain of Gag was changed). Particles are accumulating in the endoplasmic reticulum after budding into the cisternae (inset). Pm, Plasma membrane; Nu, Nucleus; ERm, Endoplasmic reticulum membrane. (C) Intracellular amplification efficiency of IAPE and modified IAPE.