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Capture in the metabolic arena: co-selection of gamma and deltaretrovirus envelope glycoproteins and their receptors

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Although all infectious and replication-competent retroviruses harbor an *env* gene, the origin of *env* remains unknown except for that of a few invertebrate retroviruses. It is generally admitted that infectious retroviruses have evolved from endogenous viral retrotransposons by insertion of an "external" gene that encodes for a fusion glycoprotein (*env* capture). In 2000, Malik *et al*. provided the first formal evidence for the origin of *env* in several invertebrate retroviruses. For instance, they showed that *env* of *Gypsy*, an infectious *Drosophila* retrotransposon, has been "captured" from a fusion protein-encoding gene of a baculovirus, a totally unrelated large DNA enveloped virus.

Vertebrate retroviruses cover 7 genera distinguished by their *gag* (capsid encoding) and *pol* (enzyme encoding) genes. The gammaretroviruses (murine leukemia viruses, MLV as a prototype) and deltaretroviruses (the human T cell leukemia virus, HTLV as a prototype) are the most distant genera according to their *pol* genes. However, we reported that HTLV *env* is most closely related to MLV *env*, sharing similar modular organization and motifs even within the receptor-binding domain (RBD), the Env most variable sequence. Accordingly, swapping the RBD-encoding regions between the two types of Env yielded functional chimeras. We argued that this common ancestry between the *env* of remotely related retroviruses is also in favor of an *env* capture scenario by vertebrate retroviruses. Nonetheless, the origin of these *env*, and more specifically their RBD, remains unknown.

Based on the gammaretrovirus Env modular organization, we derived soluble RBD domains of different gamma and deltaretroviruses. This has been instrumental to the identification of Glut1, the major glucose transporter, as the cognate receptor of HTLV-1 and 2 Env. We further showed that Glut1 binds all known HTLV or S(imian)TLV types and that intracellular interaction of HTLV or STLV RBD with Glut1 modulates glucose transport and glycolysis. Of most interest is that, like Glut1, all of the receptors identified so far for gammaretrovirus Env belong to the family of multimembrane-spanning molecules and that those for which a function has been determined are all metabolite transporters (amino acids, inorganic phosphate, vitamins, etc.).

The selection as Env receptors of metabolite transporters that shuttles from cytoplasmic pools to the cell surface and the cytoplasmic interaction between RBD and their

cognate receptors have us to postulate that gamma and deltaretrovirus Env, and more particularly their RBD modules, are related to transporter chaperone molecules that modulate their cell surface translocation.