

Invited speaker presentation

## The fallout from crossing paths with cellular cytidine deaminases

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Humans are unique in encoding eleven APOBEC cytidine deaminases that edit single stranded DNA (ssDNA). So far no other species encodes so many. To be exact, *prime face* evidence has been found for 8, the remaining 3 proving to be recalcitrant. Single stranded DNA is synonymous with replication and transcription and might suggest a role in epigenetic modification. The most widely known member goes by a different name, AID, and is responsible for class switch recombination and somatic hypermutation of rearranged immunoglobulin V region loci. Retroviral cDNA is of course, single stranded and an anti-viral activity possible. In fact the lentiviruses and one of their precursors were so vulnerable to some of the APOBEC3 enzymes that they evolved the *vif* gene more than 10 M years ago to effectively take them out. By contrast, HTLV-1 and other retroviruses seem not to be bothered. By contrast several human APOBEC3 genes do act as major restriction factors for hepatitis B virus *in vivo*. Some of the APOBEC3 genes are upregulated by interferon- $\alpha$ , which goes a long way with an anti-viral role for certain APOBEC3 members. Finally some of the human genes at least, may also restrict some other human viruses *in vivo* presumably during replication and/or transcription. Indeed, a rather eclectic ensemble.

The role of these deaminases in controlling the replication of retroviruses and endogenous retroviruses (ERVs) doesn't fit well with their phylogeny and gene copy number. For example, the mouse genome encodes only one APOBEC3 gene while humans have seven. The avian and reptile lineages are full of ERVs yet they do not encode any APOBEC3 gene. Similarly, there are no such genes in plant genomes, despite a plethora of retroviruses.

Massive retroviral hypermutation can be used as a surrogate marker for elevated expression of these deaminases *in vivo*. Given that three laws of thermodynamics shows that no machine is perfect, is it possible that over-expression of some of these cytidine deaminases results in a breakdown of the proper stoichiometry associated with APOBEC3 complexes allowing excess enzyme to turn against cellular DNA? In short, can they help push cells down the road to cancer? This is a particularly exciting idea, given that the exploding field of cancer genomics is showing that not only are there far more mutations in a cancer cell than hitherto thought ( $>10^3$ ), but also the most frequent mutation is precisely the C->T transition. The presentation will address all aspects of the above.