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Retroviral restriction factors: new mechanisms of innate immunity

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We are interested in characterizing the cellular machinery involved in the restriction of retrovirus replication - the components of the innate or "intrinsic" immunity. Studies of two such systems will be presented. In the first example, we have identified components involved in transcriptional silencing of proviral DNA by Embryonic Stem (ES) cells. It has long been known that ES cells potently block provirus expression *via* a transacting factor that binds to the primer binding site (PBS) for proline tRNA on the murine leukemia virus genome. We have purified the silencing complex and identified TRIM28 (Kap-1), a known transcriptional silencer, as an integral component of the complex. Further, we have identified the DNA sequence-specific binding component of the complex as being ZFP809, one of the dozens of zinc finger proteins encoded in the mammalian genome. We show that expression of ZFP809 is sufficient to render even differentiated cells highly resistant to MLV infection. Furthermore, we demonstrate that ZFP809 is able to potently block transcription from DNA constructs of human T-cell lymphotropic virus-1 (HTLV-1), which use the same primer tRNA. Finally, we found that similar silencing occurs at the distinct PBS for at least one other tRNA (namely, Lys1,2) utilized by such viruses as visna and spuma.

In the second example, we have identified a novel antiviral gene that prevents the accumulation of retroviral mRNAs in the cytoplasm. The gene, designated ZAP, encodes a CCCH-type zinc finger antiviral protein. A region near the 3' end of the Moloney MuLV RNA was identified as necessary and sufficient to provide sensitivity to ZAP and to target mRNAs for loss. ZAP did not affect nuclear RNA levels but dramatically shortened the half-life of the viral RNAs in the cytoplasm. ZAP also potently inhibited HIV-1 RNA accumulation. ZAP was tested for its ability to inhibit viruses from other families and was found to potently inhibit the replication of multiple members of the alphavirus genus, including Sindbis, Semliki Forest, Ross River, and Venezuelan equine encephalitis viruses. As for retroviruses, the major block to Sindbis RNA accumulation could be localized to a small portion of the genome. Recombinant ZAP was found to bind specifically to the viral RNAs in vitro, and binding efficiency correlated well with restriction activity. ZAP binds to a single subunit of the RNA exosome, the major cellular machinery for RNA turnover, suggesting that it brings the exosome to the target RNAs to degrade them.