

## TRIM5 AND THE ANTIVIRAL STATE

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TRIM5 is a host restriction factor that mediates a CA-specific block to retroviral infection. TRIM5alpha binding to the viral protein is only detectable when CA is in the multimeric protein lattice of the retroviral core. This suggested that TRIM5 might function as a pattern recognition receptor (PRR) analogous to a TLR. Additionally, *TRIM5* is located within a cluster of interferon-stimulated genes. We therefore sought evidence for functional links between TRIM5 and innate immune factors. TRIM5 was induced by type I interferons and PRR agonists in THP-1 cells and monocyte-derived dendritic cells and macrophages. Induction kinetics, knockdown of IRF3, STAT1, STAT2, or IFN $\alpha$ R, and IFN $\alpha$ R-blocking antibodies demonstrated that TRIM5alpha mRNA induction is not IRF3-dependent, but ISGF3-dependent. In parallel, we found that establishment of an antiviral state with interferon or PRR agonists prevented HIV-1 transduction of THP1 cells or monocyte-derived dendritic cells and macrophages. TRIM5 knockdown in THP1 cells rescued HIV-1 from the antiviral state established by LPS or polyIC as effectively as IRF3 knockdown. Also like the IRF3 knockdown, TRIM5 knockdown failed to rescue HIV-1 transduction from exogenous type 1 interferon. This effect of TRIM5 knockdown was independent of CA and even observed with non-retroviruses. We then showed that TRIM5 regulates and interacts with TAK1 and TRAFs that act upstream of the NF $\kappa$ B and AP-1 signaling pathways, but not upstream of IRF3. Consistent with these effects on signal transduction, stable knockdown of TRIM5 in cell lines or in primary human CD4+ T cells was associated with a pronounced defect in cell proliferation. Thus, in addition to mediating CA-specific restriction of retroviruses, TRIM5 contributes in a more general way to signal transduction and the antiviral state. Whether these two functions of TRIM5 are functionally related remains to be determined.