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How Endogenous Retroviruses Have Become an Integral Component of the Host Immune Response.

The antibody response to type 2 T-cell independent (TI-2) antigens is important for defense against infections. Initiated by B cell receptor (BCR) crosslinking in the absence of T cell help, there has been no suggestion of a requirement for innate immune signaling. However, we have discovered that cytosolic RNA and DNA sensing pathways operate within B cells to permit optimal induction of the TI-2 response. Cross-linking of the BCR by TI-2 antigens leads to upregulation of numerous endogenous retrovirus (ERV) RNAs in B cells in a Btk and NF-κB dependent manner. These RNAs are directly detected via a MAVS-dependent RNA sensing pathway, which activates NF-κB, or reverse transcribed and indirectly detected via the cGAS-cGAMP-STING pathway, triggering a second, sustained wave of signaling that promotes specific IgM production. Deficiency of both MAVS and cGAS or treatment of MAVS-deficient mice with reverse transcriptase inhibitors can dramatically inhibit TI-2 antibody responses. ERV and two innate sensing pathways that detect them are integral and essential components of the TI-2 B cell signaling apparatus. These findings suggest in turn a possible link between chronic activation of the TI-2 B cell response and cell transformation caused by retrotransposition. They also indicate that the widely discussed connection between ERV and autoimmunity may result from dysregulation of a physiological immune process.