# Tissue-restricted antigen-like expression of endogenous retroviruses in the thymus supports their role in negative selection

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Endogenous retroviruses (ERVs) are remnants of ancient viral infections that have been part of the host genome for millions of years. Despite their viral origin, ERV-derived proteins and RNA are found in healthy tissues without triggering an immune response. This raises a fundamental question: why does the immune system tolerate these foreign elements? A likely explanation is that ERVs are incorporated into immune tolerance mechanisms, preventing autoimmunity against their expression products. Since immune tolerance is established in the thymus through the negative selection of autoreactive T cells, we hypothesize that ERVs are expressed in medullary thymic epithelial cells (mTECs) and presented as self-antigens.

To test this, we analyzed single-cell RNA sequencing (scRNA-seq) data from human and mouse thymic tissues, focusing on mTECs—specialized cells that train T cells by expressing a broad set of tissue-restricted antigens (TRAs). Our results show that ERVs are actively transcribed in mTECs following a pattern similar to TRAs: the number of expressed ERV loci is significantly higher in mTECs compared to other thymic cells. We also found that younger ERV subfamilies are more transcriptionally active, and many ERV loci overlap with long non-coding RNAs (lncRNAs), some of which are linked to different pathological conditions. These findings were consistent in both humans and mice, pointing to an evolutionarily conserved role for ERVs in thymic selection.

This study provides the first locus-specific analysis of ERV expression in mTECs and suggests that ERVs may actively contribute to immune tolerance. By exposing developing T cells to ERV-derived antigens, the thymus might prevent autoimmunity against these elements later in life. Our findings challenge the view of ERVs as inactive genomic fossils and highlight their potential role in shaping immune regulation, with implications for autoimmune diseases and immune responses to ERV reactivation in disease states.